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(54) Benzazepin derivatives as vasopressin antagonists.

(57) Novel benzoheterocyclic compounds of the formula:

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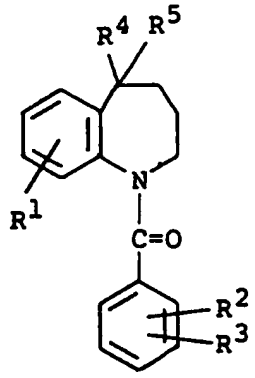
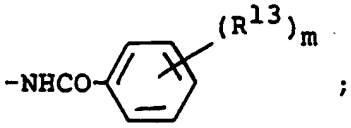


wherein R^1 is H, halogen, OH, etc,; R^2 is H, alkyl, halogen or alkoxy; R^3 is phenyl-alkanoylamino, or



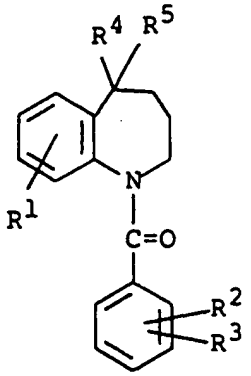
;

R^4 is H, $-NR^6R^7$, alkenyloxy, HO-alkyl, $-O-CO-A-NR^8R^9$, etc.; R^5 is H, OH, etc., or a salt thereof, which have excellent vasopressin antagonistic activities and useful as vasodilator, hypotensive agent, water diuretics, platelet agglutination inhibitor, and a vasopressin antagonistic composition containing the compound as the active ingredient.

The present invention relates to novel benzoheterocyclic compounds which have excellent vasopressin antagonistic activities and are useful as vasodilator, hypotensive agent, water diuretics, platelet agglutination inhibitor.

The benzoheterocyclic compounds of the present invention and pharmaceutically acceptable salts thereof are novel compounds which have never been dislcosed in any literature, and are useful as a medicament.

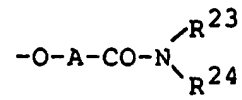
The present invention provides a benzoheterocyclic compound of the formula:



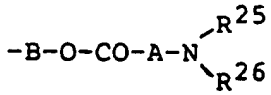
(1)

wherein R^1 is hydrogen atom; a halogen atom; hydroxy group; a lower alkanoyloxy group; an amino-lower alkoxy group which may optionally be substituted by a group selected from a lower alkyl group and a lower alkanoyl group; a carboxy-substituted lower alkoxy group; a lower alkoxycarbonyl-substituted lower alkoxy group; or an aminocarbonyl-lower alkoxy group which may optionally be substituted by a lower alkyl group,

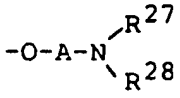
R^4 is hydrogen atom; a group of the formula: $-NR^6R^7$ (wherein R^6 and R^7 are the same or different and are hydrogen atom, a lower alkyl group or a lower alkenyl group); a lower alkenyloxy group; a hydroxy-substituted lower alkyl group; a group of the formula: $-O-CO-A-NR^8R^9$ (wherein A is a lower alkylene group, R^8 and R^9 are the same or different and are hydrogen atom or a lower alkyl group, and R^8 and R^9 may bind together with the adjacent nitrogen atom to which they bind to form a 5- or 6-membered, saturated or unsaturated heterocyclic ring which may be intervened or not with nitrogen or oxygen atom, wherein the said heterocyclic ring may optionally have a lower alkyl substituent); a group of the formula: $-O-R^{10}$ (wherein R^{10} is an amino acid residue.); a lower alkoxycarbonyl-substituted lower alkylidene group; a lower alkoxycarbonyl-substituted lower alkyl group; a carboxy-substituted lower alkyl group; a group of the formula: $-A-CONR^{11}R^{12}$ (wherein A is the same as defined above, R^{11} and R^{12} are the same or different and are hydrogen atom, a lower alkyl group, a piperidinyl group which may optionally be substituted by a phenyl-lower alkyl group on the piperidine ring, or a carbamoyl-lower alkyl group, and R^{11} and R^{12} may bind together with the adjacent nitrogen atom to which they bind to form a 5- or 6-membered, saturated heterocyclic ring which may be intervened or not with nitrogen or oxygen atom, wherein the said heterocyclic ring may optionally be substituted by a group selected from a lower alkyl group, a lower alkoxycarbonyl group and an amino group optionally having a substituent selected from a lower alkyl group and a lower alkanoyl group); a group of the formula:



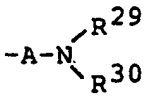
(wherein A is the same as defined above, R^{23} and R^{24} are the same or different and are hydrogen atom, a lower alkoxycarbonyl-substituted lower alkyl group, a carboxy-substituted lower alkyl group, or a piperidinyl group which may optionally be substituted by a lower alkyl group on the piperidine ring); a pyrrolidinylcarbonyl-lower alkoxy group which is substituted by a lower alkoxycarbonyl group on the pyrrolidine ring; a lower alkoxy-substituted lower alkanoyloxy group; a group of the formula:



(wherein A is the same as defined above, B is a lower alkylene group, R^{25} and R^{26} are the same or different and are hydrogen atom or a lower alkyl group); an amino-substituted lower alkylidene group wherein the amino moiety may optionally be substituted a lower alkyl group; a group of the formula:



(wherein A is the same as defined above, R^{27} and R^{28} bind together with the adjacent nitrogen atom to which they bind to form a 5- or 10-membered, saturated or unsaturated heteromonocyclic ring or heterobicyclic ring which may be intervened or not with nitrogen or oxygen atom, wherein the said heterocyclic ring may optionally be substituted by a group selected from an oxo group, a lower alkyl group, a lower alkoxycarbonyl group and a lower alkanoyl group); cyano group; a cyano-substituted lower alkyl group; a lower alkoxy group having a substituent selected from hydroxy group and a phenylsulfonyloxy group optionally being substituted by a lower alkyl group on the phenyl ring; a group of the formula:



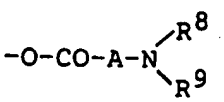
(wherein A is the same as defined above, R^{29} and R^{30} bind together with the adjacent nitrogen atom to which they bind to form a 5- or 6-membered, saturated heterocyclic ring which may be intervened or not with nitrogen or oxygen atom, wherein the said heterocyclic ring may optionally be substituted by a group selected from a lower alkyl group, a lower alkanoyl group and an amino group optionally having a lower alkyl substituent); a phenylsulfonyloxy-substituted lower alkyl group which may optionally be substituted by a lower alkyl group on the phenyl ring; a phthalimido-substituted lower alkyl group; or a cyano-substituted lower alkylidene group,

R^5 is hydrogen atom or hydroxy group, and R^4 and R^5 may combine together to form an oxo group,

R^2 is hydrogen atom, a lower alkyl group, a halogen atom or a lower alkoxy group,

R^3 is a group of the formula:

(wherein R^{13} is a halogen atom, carbamoyl group, a lower alkyl group, a piperazinyl-lower alkoxy group which is substituted by a lower alkanoyl group on the 4-position of the piperazine ring, m is 0 or an integer of 1 to 3) or a phenyl-lower alkanoylamino group which is substituted by 1 to 3 groups selected from a halogen atom, a lower alkoxy group, a lower alkyl group and nitro group on the phenyl ring, provided that when R^1 is hydrogen atom or a halogen atom, R^4 is hydrogen atom, a group of the formula: $-NR^6R^7$ - (wherein R^6 and R^7 are the same as defined above),
a group of the formula:



(wh r in A is the same as d fin d above, and R^8 and R^9 are the sam or different and are hydrogen atom or a lower alkyl group) or a hydroxy-substituted low r alkyl group, and R^5 is hydrogen atom, hydroxy group or R^4 and R^5 combine together to form an oxo group, R^3 is a group of the formula:

(wherein R^{13} is carbamoyl group, or a piperazinyl-lower alkoxyl group which is substituted by a lower alkanoyl group on the 4-position of the piperazine ring, and m is the same as defined above), or a salt thereof.

The present inventors have intensively studied and have found that the benzoheterocyclic compounds and salts thereof of the present invention have excellent vasopressin antagonistic activities.

The benzoheterocyclic compounds of the formula (1) and their salts of the present invention have excellent vasopressin antagonistic activities and vasodilating activity, hypotensive activity, activity for inhibiting saccharide release in liver, activity for inhibiting growth of mesangium cells, water diuretic activity, platelet agglutination inhibitory activity and are useful as vasodilator, hypotensive agent, water diuretics, platelet agglutination inhibitor in the treatment or prophylaxis of hypertension, edema, ascites, heart failure, renal function disorder, vasopressin parasecretion syndrome (SIADH), hepatocirrhosis, hyponatremia, hypokaliemia, diabetic, circulation disorder, and the like.

Each group in the above formula (1) includes specifically the following groups.

The "lower alkoxy" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, and the like.

The "lower alkyl" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl, and the like.

The "halogen atom" includes fluorine atom, chlorine atom, bromine atom, and iodine atom.

The "lower alkenyl" includes a straight chain or branched chain alkenyl group having 2 to 6 carbon atoms, for example, vinyl, allyl, 2-butenyl, 3-butenyl, 1-methylallyl, 2-pentenyl, 2-hexenyl, and the like.

The "lower alkenyloxy" includes a straight chain or branched chain alkenyloxy group having 2 to 6 carbon atoms, for example, vinyloxy, allyloxy, 2-butenyloxy, 3-butenyloxy, 1-methylallyloxy, 2-pentenyloxy, 2-hexenyloxy, and the like.

The "lower alkylene" includes a straight or branched chain alkylene group having 1 to 6 carbon atoms, for example, methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene, hexamethylene, and the like.

The "lower alkanoyloxy" includes a straight chain or branched chain alkanoyloxy group having 1 to 6 carbon atoms, for example, formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pentanoyloxy, tert-butylcarbonyloxy, hexanoyloxy, an the like.

The "hydroxy-substituted lower alkyl" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by 1 to 3 hydroxy groups, for example, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxyethyl, 4-hydroxybutyl, 3,4-dihydroxybutyl, 1,1-dimethyl-2-hydroxyethyl, 5-hydroxypentyl, 6-hydroxyhexyl, 2-methyl-3-hydroxypropyl, 2,3,4-trihydroxybutyl, and the like.

The "aminocarbonyl-lower alkoxy which has a lower alkyl substituent" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which has an aminocarbonyl groups being substituted by 1 to 2 straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methylaminocarbonylmethoxy, 1-ethylaminocarbonylethoxy, 2-propylaminocarbonylethoxy, 3-isopropylaminocarbonylpropoxy, 4-butylaminocarbonylbutoxy, 5-pentylaminocarbonylpentyloxy, 6-hexylaminocarbonylhexyloxy, dimethylaminocarbonylmethoxy, 3-diethylaminocarbonylpropoxy, diethylaminocarbonylmethoxy, (N-ethyl-N-propylamino)carbonylmethoxy, 2-(N-methyl-N-hexylamino)-carbonylethoxy, and the like.

The "lower alkoxylcarbonyl-substituted lower alkyl" includes a straight chain or branch d chain having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms, for example, methoxycarbonylmethyl, 3-methoxycarbonylpropyl, ethoxycarbonylmethyl, 3-ethoxycarbonylpropyl, 4- thoxycarbonylbutyl, 5-isopropoxycarbonylpentyl, 6-propoxycarbonylhexyl, 1,1-

dimethyl-2-butoxycarbonylethyl, 2-methyl-3-t rt-butoxycarbonylpropyl, 2-pentyloxycarbonylethyl, hexyloxycarbonylmethyl, and the like.

The "carboxy-substituted lower alkyl" includes a carboxyalkyl group wherein the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, carboxymethyl, 2-carboxyethyl, 1-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxypentyl, 6-carboxyhexyl, 1,1-dimethyl-2-carboxyethyl, 2-methyl-3-carboxypropyl, and the like.

The "phenyl-lower alkanoylamino which is substituted by 1 to 3 groups selected from a halogen atom, a lower alkoxy, a lower alkyl or nitro on the phenyl ring" includes phenylalkanoylamino group wherein the alkanoyl moiety is a straight chain or branched chain alkanoyl group having 2 to 6 carbon atoms, and which is substituted by 1 to 3 groups selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, a halogen atom and nitro group on the phenyl ring, for example, 2-methoxyphenylacetylamino, 3-methoxyphenylacetylamino, 4-methoxyphenylacetylamino, 3-(2-ethoxyphenyl)propionylamino, 2-(3-ethoxyphenyl)-propionylamino, 4-(4-ethoxyphenyl)butyrylamino, 2,2-dimethyl-3(4-isopropoxyphenyl)propionylamino, 5-(4-pentyloxyphenyl)pentanoylamino, 2,4-dimethoxyphenylacetylamino, 4-hexyloxyphenylacetylamino, 3,4-dimethoxyphenylacetylamino, 2-(3-ethoxy-4-methoxyphenyl)propionylamino, 3-(2,3-dimethoxyphenyl)-propionylamino, 4-(3,4-diethoxyphenyl)butyrylamino, 2,5-dimethoxyphenylacetylamino, 6-(2,6-dimethoxyphenyl)hexanoylamino, 3,5-dimethoxyphenylacetylamino, 3,4-dipentyloxyphenylacetylamino, 3,4,5-trimethoxyphenylacetylamino, 2-chlorophenylacetylamino, 3-chlorophenylacetylamino, 4-chlorophenylacetylamino, 2-fluorophenylacetylamino, 3-fluorophenylacetylamino, 3-(4-fluorophenyl)-propionylamino, 2-(2-bromophenyl)propionylamino, 4-(3-bromophenyl)butyrylamino, 5-(4-bromophenyl)-pentanoylamino, 6-(2-iodophenyl)hexanoylamino, 3-iodophenylacetylamino, 3-(4-iodophenyl)propionylamino, 4-(3,4-dichlorophenyl)butyrylamino, 3,4-dichlorophenylacetylamino, 2,6-dichlorophenylacetylamino, 2,3-dichlorophenylacetylamino, 2,4-dichlorophenylacetylamino, 3,4-difluorophenylacetylamino, 3-(3,5-dibromophenyl)propionylamino, 3,4,5-trichlorophenylacetylamino, 2-methoxy-3-chlorophenylacetylamino, 2-methylphenylacetylamino, 3-methylphenylacetylamino, 4-methylphenylacetylamino, 3-(2-ethylphenyl)-propionylamino, 2-(3-ethylphenyl)propionylamino, 4-(4-ethylphenyl)butyrylamino, 5-(4-isopropylphenyl)-pentanoylamino, 6-(3-butylphenyl)hexanoylamino, 3-(4-pentylphenyl)propionylamino, 4-hexylphenylacetylamino, 3,4-dimethylphenylacetylamino, 3,4-diethylphenylacetylamino, 2,4-dimethylphenylacetylamino, 2,5-dimethylphenylacetylamino, 2,6-dimethylphenylacetylamino, 3,4,5,-trimethylphenylacetylamino, 3-chloro-4-methylphenylacetylamino, 3-methoxy-4-methyl-5-iodophenylacetylamino, 3,4-dimethoxy-5-bromophenylacetylamino, 3,5-diiodo-4-methoxyphenylacetylamino, 2-nitrophenylacetylamino, 3-nitrophenylacetylamino, 3,4-dinitrophenylacetylamino, 3,4,5-trinitrophenylacetylamino, and the like.

The "lower alkoxycarbonyl-substituted lower alkylidene" includes a straight chain or branched chain alkylidene group having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms, for example, ethoxycarbonylmethylidene, 2-methoxycarbonylethylidene, 3-isopropoxycarbonylpropylidene, 2-propoxycarbonylisopropylidene, 4-butoxycarbonylbutylidene, 5-pentyloxycarbonylpentylidene, 6-hexyloxycarbonylhexylidene, and the like.

The "5- or 6-membered, saturated or unsaturated heterocyclic ring which is formed by binding the groups of R^8 and R^9 together with the nitrogen atom to which they bind and may be intervened or not with nitrogen or oxygen atom" includes, for example, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, pyrrolyl, imidazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, pyrazolyl, 2-pyrrolyl, 2-imidazolynyl, imidazolydinyl, 2-pyrazolynyl, pyrazolydinyl, 1,2-dihydropyridyl, 1,2,3,4-tetrahydropyridyl, and the like.

The "above mentioned heterocyclic ring which is substituted by lower alkyl groups" includes the above mentioned heterocyclic rings being substitututed by 1 to 3 straight chain or branched chain alkyl groups having 1 to 6 carbon atoms, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrodinyl, 2-propylpyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butylpiperidinyl, 3-pentylmorpholino, 4-hexylpiperazinyl, 2-methylimidazolyl, 3-methyl-1,2,4-triazolyl, 3-methylpyrrolyl, 3-methylpyrazolyl, 4-methyl-1,2-dihydropyridyl, and the like.

The "amino acid residue" includes, for example, alanyl, β-alanyl, arginyl, cistathionyl, cystyl, glycyl, histidyl, homoseryl, isoleucyl, lanthionyl, leucyl, lysyl, methionyl, norleucyl, norvalyl, ornithyl, prolyl, sarcosyl, celyl, threonyl, thyronyl, tyrosyl, valyl, α-aspartyl, β-aspartyl, aspartoyl, asparaginyl, α-glutamyl, γ-glutamyl, glutaminyl, cisteinyl, homocisteinyl, tryptophyl, dim thylglycyl, and the like.

The "amino-lower alkoxyl which may optionally be substituted by a group selected from a lower alkyl and a lower alkanoyl" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by an amino group optionally having 1 to 2 substituents selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms and a straight chain or branched chain alkanoyl group having 1 to 6 carbon atoms, for example, aminom thoxy, 2-aminoethoxy, 1-aminoethoxy, 3-

aminopropoxy, 4-aminobutoxy, 5-aminop ntyloxy, 6-aminoh xyloxy, 1,1-dim thyl-2-amino thoxy, 2-m thyl-3-aminopropoxy, ac tylaminomethoxy, 1-acetylaminoethoxy, 2-propionylamino thoxy, 3-isopropionylaminopropoxy, 4-butyrylaminobutoxy, 5-pentanoylaminopentyloxy, 6-hexanoylaminohexyloxy, formylaminomethoxy, methylaminomethoxy, 1-ethylaminoethoxy, 2-propylaminoethoxy, 3-isopropylaminopropoxy, 4-butylaminobutoxy, 5-pentylaminopentyloxy, 6-hexylaminohexyloxy, dimethylaminomethoxy, (N-ethyl-N-propylamino)methoxy, 2-(N-methyl-N-hexylamino)ethoxy, and the like.

The "lower alkoxycarbonyl-substituted lower alkoxy" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms, for example, methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy,ethoxycarbonylmethoxy, 3-ethoxycarbonylpropoxy, 4-ethoxycarbonylbutoxy, 5-isopropoxycarbonylpentyloxy, 6-propoxycarbonylhexyloxy, 1,1-dimethyl-2-butoxycarbonylethoxy, 2-methyl-3-tert-butoxycarbonylpropoxy, 2-pentyloxycarbonylethoxy, hexyloxycarbonylmethoxy, and the like.

The "carboxy-substituted lower alkoxy" includes a carboxyalkoxy group wherein the alkoxy moiety is a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, carboxymethoxy, 2-carboxyethoxy, 1-carboxyethoxy, 3-carboxypropoxy, 4-carboxybutoxy, 5-carboxypentyloxy, 6-carboxyhexyloxy, 1,1-dimethyl-2-carboxyethoxy, 2-methyl-3-carboxypropoxy, and the like.

The "piperidinyl which may optionally be substituted by a phenyl-lower alkyl on the piperidine ring" includes a piperidinyl group which may optionally be substituted by a phenylalkyl group on the piperidine ring wherein the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, piperidinyl, 1-benzyl-4-piperidinyl, 1-(2-phenylethyl)-3-piperidinyl, 1-(1-phenylethyl)-2-piperidinyl, 1-(3-phenylpropyl)-4-piperidinyl, 1-(4-phenylbutyl)-4-piperidinyl, 1-(5-phenylpentyl)-4-piperidinyl, 1-(6-phenylhexyl)-4-piperidinyl, 1-(1,1-dimethyl-2-phenylethyl)-3-piperidinyl, 1-(2-methyl-3-phenylpropyl)-2-piperidinyl, and the like.

The "carbamoyl-lower alkyl" includes a carbamoylalkyl group wherein the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, carbamoylmethyl, 2-carbamoylethyl, 1-carbamoylethyl, 3-carbamoylpropyl, 4-carbamoylbutyl, 5-carbamoylpentyl, 6-carbamoylhexyl, 1,1-dimethyl-2-carbamoylethyl, 2-methyl-3-carbamoylpropyl, and the like.

The "lower alkanoyl" includes a straight chain or branched chain alkanoyl group having 1 to 6 carbom atoms, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, hexanoyl, and the like.

The "amino which may optionally be substituted by a group selected from a lower alkyl and a lower alkanoyl" includes an amino group optionally being substituted by 1 to 2 groups selected from a straight chain or branched chain alkyl having 1 to 6 carbon atoms and a straight chain or branched chain alkanoyl having 1 to 6 carbon atoms, for example, amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, N-methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, N-methyl-N-hexylamino, N-methyl-N-acetylamino, N-acetylamino, N-formylamino, N-propionylamino, N-butyrylamino, N-isobutyrylamino, N-pentanoylamino, N-tert-butylcarbonylamino, N-hexanoylamino, N-ethyl-N-acetylamino, and the like.

The "lower alkoxycarbonyl-substituted lower alkyl" includes a straight chain or branched chain akyl group having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkoxycarbonyl having 1 to 6 carbon atoms, for example, methoxycarbonylmethyl, 3-methoxycarbonylpropyl, ethoxycarbonylmethyl, 3-ethoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 5-isopropoxycarbonylpentyl, 6-propoxycarbonylhexyl, 1,1-dimethyl-2-butoxycarbonylethyl, 2-methyl-3-tert-butoxycarbonylpropyl, 2-pentyloxycarbonylethyl, hexyloxycarbonylmethyl, and the like.

The "carboxy-substituted lower alkyl" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by a carboxy, for example, carboxymethyl, 2-carboxyethyl, 1-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxypentyl, 6-carboxyhexyl, 1,1-dimethyl-2-carboxyethyl, 2-methyl-3-carboxypropyl, and the like.

The "piperidinyl optionally having a lower alkyl substituent on the piperidine ring" includes a piperidinyl group optionally being substituted by a straight chain or branched chain alkyl having 1 to 6 carbon atoms on the piperidine ring, for example, piperidinyl, 1-methyl-4-piperidinyl, 1-ethyl-3-piperidinyl, 1-propyl-2-piperidinyl, 1-butyl-4-piperidinyl, 1-pentyl-4-piperidinyl, 1-hexyl-4-pip ridinyl, and the lik .

The "pyrrolidinylcarbonyl-lower alkoxy having a low r alkoxycarbonyl on the pyrrolidin ring" includes a pyrrolidinylcarbonylalkoxy group wher in the alkoxy moiety is a straight chain or branched chain alkoxy having 1 to 6 carbon atoms, and which is substituted by a straight chain or branched chain alkoxycarbonyl having 1 to 6 carbon atoms on the pyrrolidine ring, for example, 2-methoxycarbonyl-1-pyrrolidinylcarbonylm thoxy, 1-(2-ethoxycarbonyl-1-pyrrolidinylcarbonyl)ethoxy, 2-(3-propoxycarbonyl-1-pyr-

rolidinylcarbonyl)ethoxy, 3-(2-butoxycarbonyl-1-pyrrolidinylcarbonyl)propoxy, 4-(3-pentyloxycarbonyl-1-pyrrolidinylcarbonyl)butoxy, 5-(2-hexyloxycarbonyl-1-pyrrolidinylcarbonyl)p ntyloxy, 6-(2-methoxycarbonyl-1-pyrrolidinylcarbonyl)hexyloxy, and the like.

The "lower alkoxycarbonyl" includes a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like.

The "lower alkoxy-substituted lower alkanoyloxy" includes a straight chain or branched chain alkanoyloxy having 2 to 6 carbon atoms which is substituted by a straight chain or branched chain alkoxy having 1 to 6 carbon atoms, for example, methoxyacetyloxy, 3-ethoxypropionyloxy, 2-propoxypropionyloxy, 4-butoxybutyryloxy, 2,2-dimethyl-3-pentyloxypropionyloxy, 5-hexyloxypentanoyloxy, 6-methoxyhexanoyloxy, and the like.

The "amino which is optionally be substituted by a lower alkyl" includes an amino group optionally being substituted by 1 to 2 straight chain or branched chain alkyl groups having 1 to 6 carbon atoms, for example, amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, N-methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, N-methyl-N-hexylamino, and the like.

The "amino-substituted lower alkylidene which is optionally be substituted by a lower alkyl" includes an amino-substituted straight chain or branched chain alkylidene group having 1 to 6 carbon atoms wherein the amino moiety may optionally be substituted by 1 to 2 straight chain or branched chain alkyl groups having 1 to 6 carbon atoms, for example, aminomethylidene, 2-ethylaminoethylidene, 3-propylaminopropylidene, 2-isopropylaminopropylidene, 4-butylaminobutylidene, 5-pentylaminopentylidene, 6-hexylaminohexylidene, 3-dimethylaminopropylidene, 3-(N-methyl-N-butylamino)propylidene, 2-dipentylaminoethylidene, 4-(N-methyl-N-hexylamino)butylidene, and the like.

The "cyano-substituted lower alkyl" includes a cyanoalkyl group wherein the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl, 4-cyanobutyl, 5-cyanopentyl, 6-cyanohexyl, 1,1-dimethyl-2-cyanoethyl, 2-methyl-3-cyanopropyl, and the like.

The "phthalimido-substituted alkyl" includes a phthalimido-substituted alkyl group wherein the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, phthalimidomethyl, 2-phthalimidoethyl, 1-phthalimidoethyl, 3-phthalimidopropyl, 4-phthalimidobutyl, 5-phthalimidopentyl, 6-phthalimidohexyl, 1,1-dimethyl-2-phthalimidoethyl, 2-methyl-3-phthalimidopropyl, and the like.

The "lower alkoxy group having a substituent selected from hydroxy group and a phenylsulfonyloxy group optionally being substituted by a lower alkyl group on the phenyl ring" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by 1 to 3 groups selected from hydroxy group and a phenylsulfonyloxy group optionally being substituted by 1 to 3 alkyl groups having 1 to 6 carbon atoms on the phenyl ring, for example, (2-methylphenylsulfonyloxy)methoxy, 2-(4-methylphenylsulfonyloxy)ethoxy, 3-(phenylsulfonyloxy)propoxy, 4-(3-methylphenylsulfonyloxy)butoxy, 5-(2-ethylphenylsulfonyloxy)pentyloxy, 6-(3-propylphenylsulfonyloxy)hexyloxy, (4-butylphenylsulfonyloxy)-methoxy, 2-(2-pentylphenylsulfonyloxy)ethoxy, 1-(3-hexylphenylsulfonyloxy)ethoxy, 3-(3,4-dimethylphenylsulfonyloxy)propoxy, 2-(3,4,5-trimethylphenylsulfonyloxy)ethoxy, hydroxymethoxy, 2-hydroxyethoxy, 1-hydroxyethoxy, 3-hyroxypropoxy, 2,3-dihydropropoxy, 4-hydroxybutoxy, 3,4-dihydroxybutoxy, 1,1-dimethyl-2-hydroxyethoxy, s-hydroxypentyloxy, 6-hydroxyhexyloxy, 2-methyl-3-hydroxypropoxy, 2,3,4-trihydroxybutoxy, and the like.

The "phenylsulfonyloxy-substituted lower alkyl which may optionally be substituted by a lower alkyl on the phenyl ring" includes a phenylsulfonyloxy-substituted straight chain or branched chain alkyl group having 1 to 6 carbon atoms wherein the phenylsulfonyloxy moiety may optionally be substituted by 1 to 3 straight chain or branched chain alkyl groups having 1 to 6 carbon atoms on the phenyl ring, for example, (2-methylphenylsulfonyloxy)methyl, 2-(4-methylphenylsulfonyloxy)ethyl, 3-(phenylsulfonyloxy)propyl, 4-(3-methylphenylsulfonyloxy)butyl, 5-(2-ethylphenylsulfonyloxy)pentyl, 6-(3-propylphenylsulfonyloxy)hexyl, (4-butylphenylsulfonyloxy)methyl, 2-(2-pentylphenylsulfonyloxy)ethyl, 1-(3-hexylphenylsulfonyloxy)ethyl, 3-(3,4-dimethylphenylsulfonyloxy)propyl, 2-(3,4,5-trim thylphenylsulfonyloxy)ethyl, and the like.

The "5- or 6-member d, saturat d h terocyclic ring which is formed by binding R^{11} and R^{12} or R^{29} and R^{30} together with the nitrogen atom to which they bind and may b intervened or not with nitrog n or oxygen atom" includes, for example, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, and the like.

The "above mentioned heterocyclic group which is substituted by a lower alkyl, a lower alkoxycarbonyl or an amino group optionally having substituents s lected from a low r alkyl and a lower alkanoyl" includes

the above mentioned heterocyclic groups having 1 to 3 substituents selected from a straight chain or branched chain alkyl having 1 to 6 carbon atoms, a straight chain or branched chain alkoxycarbonyl having 1 to 6 carbon atoms, and an amino group optionally being substituted by 1 to 2 groups selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms and a straight chain or branched chain alkanoyl groups having 1 to 6 carbon atoms, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butylpiperidinyl, 3-pentylmorpholino, 4-hexylpiperazinyl, 4-tert-butoxycarbonylpiperazinyl, 4-ethoxycarbonylpiperidinyl, 2-methoxycarbonylpyrrolidinyl, 3-pentyloxycarbonylmorpholino, 4-hexyloxycarbonylpiperazinyl, 4-acetylaminopiperidinyl, 4-dimethylaminopiperidinyl, 3-methylaminomorpholino, 2-aminopyrrolidinyl, 3-(N-methyl-N-hexylamino)-piperazinyl, 4-(N-methyl-N-acetylamino)piperidinyl, and the like.

The "above mentioned heterocyclic group which is substituted by a lower alkyl, a lower alkanoyl or an amino optionally being substituted by a lower alkyl" includes the above mentioned heterocyclic having 1 to 3 substituents selected from a straight chain or branched chain alkyl having 1 to 6 carbon atoms, a straight chain or branched chain alkanoyl having 1 to 6 carbon atoms, or an amino group optionally being substituted by 1 to 2 straight chain or branched chain alkyl having 1 to 6 carbon atoms, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butylpiperidinyl, 3-pentylmorpholino, 4-hexylpiperazinyl, 4-acetylpiperazinyl, 4-hexanoylpiperidinyl, 4-formylpiperidinyl, 2-propionylpyrrolidinyl, 3-butyrylmorpholino, 4-pentanoylpiperazinyl, 4-ethylaminopiperidinyl, 4-dimethylaminopiperidinyl, 3-methyl-4-acetylpiperazinyl, 3-methylaminomorpholino, 2-aminopyrrolidinyl, 3-(N-methyl-N-hexylamino)piperazinyl, 4-(N-methyl-N-butylamino)piperidinyl, and the like.

The "5- or 10-membered, saturated or unsaturated heteromonocyclic ring or heterobicyclic ring which is formed by binding R^{27} and R^{28} together with the nitrogen atom to which they bind and may be intervened or not with nitrogen or oxygen atom" includes, for example, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, imidazolyl, isoindolyl, 1,2,3,4,5,6,7-octahydroisoindolyl, and the like.

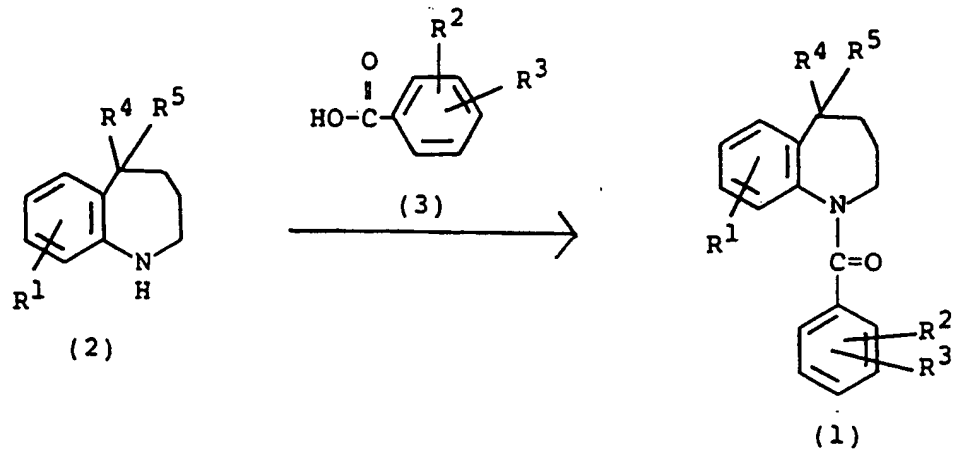
The "above mentioned heterocyclic group which is substituted by oxo group, a lower alkyl, a lower alkoxycarbonyl or a lower alkanoyl" includes the above mentioned heterocyclic groups having 1 to 3 substituents selected from oxo group, a straight chain or branched chain alkyl having 1 to 6 carbon atoms, a straight chain or branched chain alkoxycarbonyl having 1 to 6 carbon atoms, and a straight chain or branched chain alkanoyl having 1 to 6 carbon atoms, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butylpiperidinyl, 3-pentylmorpholino, 4-hexylpiperazinyl, 2-methylmorpholino, 4-formylpiperidinyl, 4-acetylpiperazinyl, 2-propanoylmorpholino, 3-butyrylmorpholino, 3-pentanoylpyrrolidinyl, 4-hexanoylpiperidinyl, 3-methyl-4-acetylpiperazinyl, 3-methylimidazolyl, 2-acetylimidazolyl, 4-tert-butoxycarbonylpiperazinyl, 4-ethoxycarbonylpiperidinyl, 2-methoxycarbonylpyrrolidinyl, 3-pentyloxycarbonylmorpholino, 4-hexyloxycarbonylpiperazinyl, 3-tert-butoxycarbonylimidazolyl, 1,3-dioxo-1,2,3,4,5,6,7-octahydroisoindolyl, and the like.

The "cyano-substituted lower alkylidene" includes a straight chain or branched chain alkylidine group having 1 to 6 carbon atoms which is substituted by cyano group, for example, cyanomethylidene, 2-cyanoetylidene, 3-cyanopropylidene, 2-cyanopropylidene, 4-cyanobutylidene, 5-cyanopentylidene, 6-cyanohexylidene, and the like.

The "piperazinyl-lower alkoxy having a lower alkanoyl at the 4-position of the piperazine ring" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by a peperazinyl being substituted by a straight chain or branched chain alkanoyl having 1 to 6 carbon atoms on the 4-position of the piperazine ring, for example, 3-(4-acetyl-1-piperazinyl)propoxy, 2-(4-acetyl-1-piperazinyl)ethoxy, (4-acetyl-1-piperazinyl)methoxy, 1-(4-propionyl-1-piperazinyl)ethoxy, 4-(4-butyryl-1-piperazinyl)butoxy, 5-(4-pentanoyl-1-piperazinyl)pentyloxy, 6-(4-hexanoyl-1-piperazinyl)hexyloxy, 3-(4-formyl-1-piperazinyl)propoxy, and the like.

The benzoheterocyclic compounds of the present invention can be prepared by various processes, for example, by the processes shown in the following reaction schemes.

[Reaction Scheme-1]



[wherein R^1, R^2, R^3, R^4 and R^5 are the same as defined above]

The process of Reaction Scheme-1 is carried out by reacting a benzoheterocyclic compound of the formula (2) and a carboxylic acid of the formula (3) by a conventional amido bond producing reaction. The amido bond producing reaction can be carried out under the conditions for the conventional amido bond producing reaction, for example,

(i) a mixed acid anhydride process, i.e. a process of reacting a carboxylic acid (3) with an alkylhalocarboxylic acid to form a mixed acid anhydride and reacting the resultant with an amine compound (2);
(ii) an acitivated ester process, i.e. a process of converting a carboxylic acid (3) into an activated ester such as p-nitrophenyl ester, N-hydroxysuccinimide ester and 1-hydroxybenzotriazole ester, etc., and reacting the resultant with an amine compound (2);
(iii) a carbodiimide process, i.e. a process of condensing a carboxylic acid (3) and an amine compound (2) in the presence of an activating agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, etc.;
(iv) other processes, i.e. a process of converting a carboxylic acid (3) into a carboxylic anhydride by treating it with a dehydrating agent such as acetic anhydride, and reacting the resultant with an amine compound (2); a process of reacting an ester of a carboxylic acid (3) with a lower alcohol and an amine compound (2) at a high temperature under high pressure; a process of reacting an acid halide compound of a carboxylic acid (3), e.g. a carboxylic acid halide, with an amine compound (2), and the like.

The mixed acid anhydride used in the above mixed acid anhydride process (i) is obtained by the known Schötten-Baumann reaction, and the reaction product is used without isolation from the reaction mixture for the reaction with the amine compound (2) to give the desired benzoheterocyclic compounds (1) of the present invention. The Schötten-Baumann reaction is usually carried out in the presence of a basic compound. The basic compound is any conventional compounds used for the Schötten-Baumann reaction and includes, for example, organic basic compounds such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonen-5 (DBN), 1,8-biazabicyclo[5.4.0]-undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc., and inorganic basic compounds such as potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, etc. The reaction is usually carried out at about -20 to about 100°C, preferably at about 0 to about 50°C, for about 5 minutes to about 10 hours, preferably for about 5 minutes to about two hours.

The reaction of thus obtained mixed acid anhydride with the amine compound (2) is usually carried out at about -20 to about 150°C, preferably at about 10 to about 50°C, for about 5 minutes to about 10 hours, preferably for about 5 minutes to about 5 hours. The mixed acid anhydride process is usually carried out in an appropriate solvent. The solvent is any conventional solvent used for the mixed acid anhydride process, and includes, for example, halogenated hydrocarbons (e.g. chloroform, dichloromethane, dichloroethane, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, tc.), ethers (e.g. diethyl ether, diisopropyl ether, tetrahydrofuran, dimethoxyethane, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, dimethylsulfoxide, acetonitrile, hexamethylphosphoric acid triamide, etc.), or a mixture of these solvents. The alkylhalocarboxylic acid us d in the mixed acid anhydride process includes, for example, methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, isobutyl chloroformate, and th lik . In said process, the carboxylic acid (3), th alkylhalocarboxylic

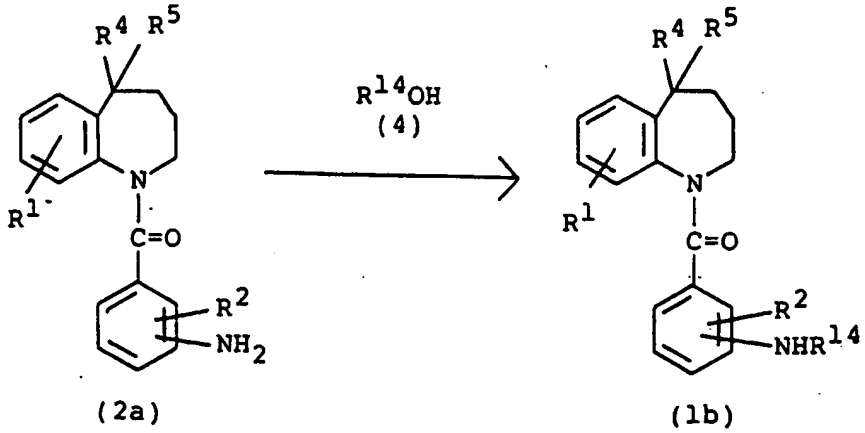
acid and th amin compound (2) are usually used in each quimolar amount, but the alkylhalocarboxylic acid and th carboxylic acid (3) can b used ach in an amount of about 1 t 1.5 mol to 1 mole of the amine compound (2).

Among the above other processes (iv), in case of the process of reacting the carboxylic acid halide with the amine compound (2), the reaction is usually carried out in the presence of a basic comopund in an appropriate solvent. The basic compound is any conventional basic compound, and includes, for example, in addition to the basic compounds used for the above mentioned Schotten-Baumann reaction, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, and the like. The solvent includes, for example, in addition to the solvents used for the above mentioned mixed acid anhydride process, alcohols (e.g. methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethylcellosolve, methylcellosolve, etc.), pyridine, acetone, water, and the like. The amount of the amine compound (2) and the carboxylic acid halide is not critical, but the carboxylic acid halide is usually used at least in equimolar amount, preferably about 1 to 5 moles to 1 mole of the amine compound (2). The reaction is usually carried out at about -20 to about 180°C, preferably at about 0 to about 150°C, for about 5 minutes to about 30 hours.

The amido bond producing reaction of Reaction Scheme-1 may also be carried out by reacting the carboxylic acid compound (3) with the amine compound (2) in the presence of a condensing agent such as phosphorus compunds (e.g. triphenylphosphine, diphenylphosphinyl chloride, phenyl-N-phenyl-phosphoramide chloridate, diethyl chlorophosphate, diethyl cyanophosphate, diphenylphosphoric acid azide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, etc.).

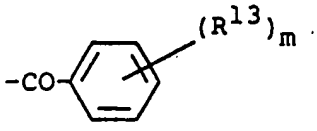
The reaction is usually carried out in the presence of a solvent and a basic compound as used in the above reaction of the carboxylic acid halide and the amine compound (2) at about -20 to about 150°C, preferably at about 0 to about 100°C, for about 5 minutes to about 30 hours. The condensing agent and the carboxylic acid (3) are used in each equimolar ammount, preferably in an amount of 1 mole to 2 moles, to 1 mole of the amine compound (2).

[Reaction Scheme-2]



(2a) (1b)

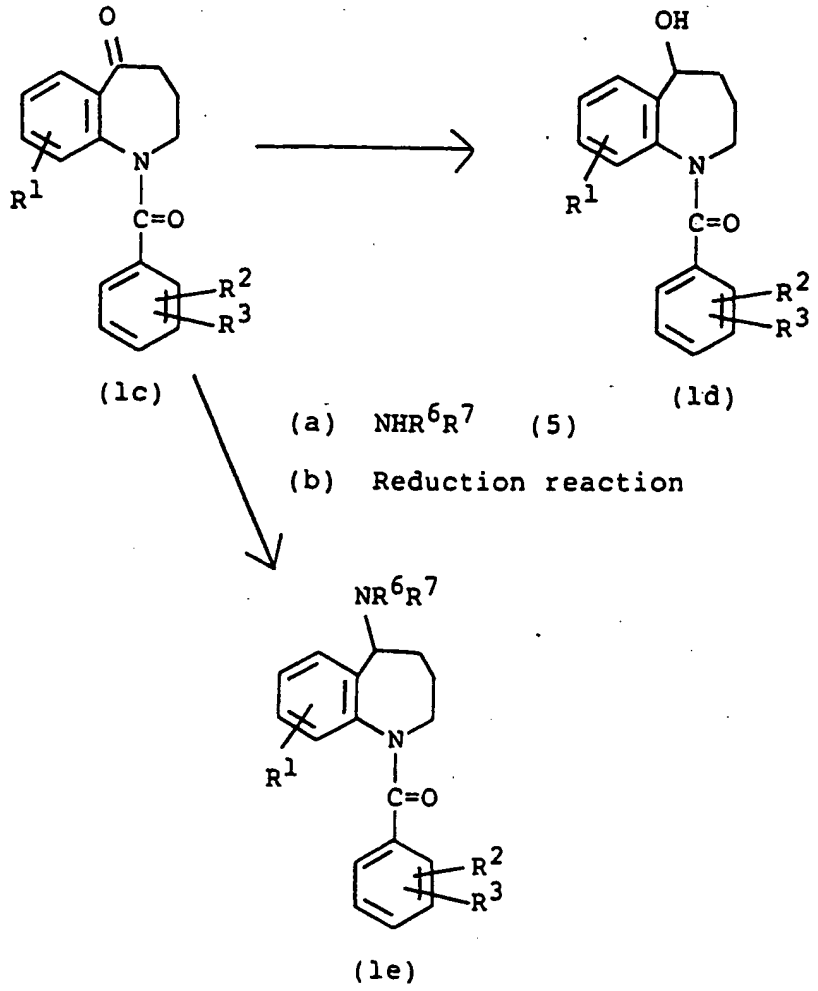
[wherein R^1, R^2, R^4 and R^5 are the same as defined above, and R^{14} is a group of the formula:



(wherein R^{13} and m are the sam as defined above), or a phenyl-lower alkanoyl group having 1 to 3 substituents on th phenyl ring selected from a halogen atom, a lower alkoxy group, a lower alkyl group and nitro group]

The reaction between the compound (2a) and the compound (4) can be carri d out under the same conditions as in the r action of th compound (2) and the compound (3) in Reaction Scheme-1.

[R action Scheme-3]



[wherein R^1, R^2, R^3, R^6 and R^7 are the same as defined above]

The reaction of converting the compound (1c) to the compound (1d) is carried out by reduction.

The above reduction reaction is preferably carried out by a process using an hydrogenation agent. The hydrogenation agent includes, for example, lithium aluminum hydride, lithium borohydride, sodium borohydride, diborane, and the like. The hydrogenation agent is used at least in equimolar amount, preferably in an amount of 1 mole to 15 moles, to 1 mole of the starting compound. The said reduction reaction is usually carried out in an appropriate solvent such as lower alcohols (e.g. water, methaonl, ethanol, isopropanol, etc.), ethers (e.g. tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme, etc.), or a mixture of these solvents. The reaction is usually carried out at about -60 to about 150 °C, preferably at -30 to 100 °C, for about 10 minutes to about 15 hours. When lithium aluminum hydride or diborane is used as a reducing agent, the non-aqueous solvent such as tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme, etc. is preferable.

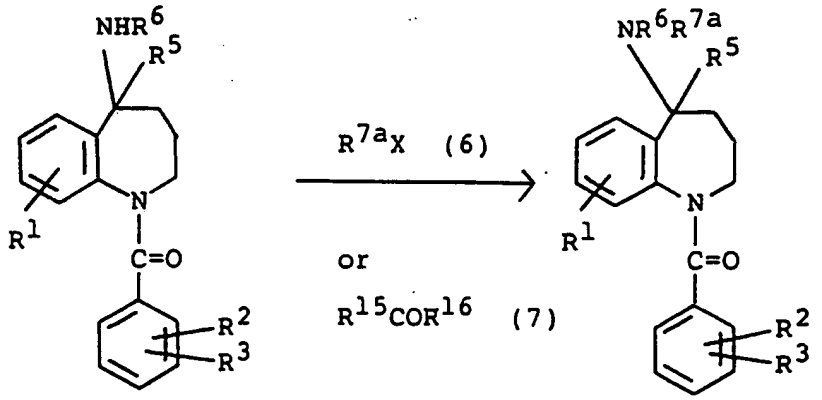
The process of converting the compound (1c) to the compound (1e) is usually carried out in an appropriate solvent or without solvent in the presence or absence of a dehydrating agent. The solvent includes, for example, alcohols (e.g. methanol, ethanol, isopropanol, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc.), aprotic polar solvents (e.g. dimethylformamide, dimethylacetamide, N-methylpyrrolidone, etc.), or a mixture of these solvents. The dehydrating agent includes, for xample, any conventional drying agent used for dehydration of solvent (e.g. molecular shiev s, tc.), mineral acids (e.g.

hydrochloric acid, sulfuric acid, boron trifluoride, tc.), organic acids (.g. p-tolu nesulfonic acid, tc.), and the like. The said reaction is usually carri d out at a temperatur of from room temperatur to 250°C, preferably at about 50 to about 200°C, for about 1 to about 48 hours. The amount of the compound (5) is not critical, but the compound (5) is used at least in equimolar amount, preferably in an amount of 1 mole to large excess amount, to 1 mole of the compound (1c). When a drying agent is used as a dehydrating agent, it should be used in large excess amount, and when an acid is used as a dehydrating agent, it should be used in a catalytic amount.

The subsequent reduction reaction may be carried by various processes, and is carried out by catalytic hydrogenation with a catalyst in an appropriate solvent. The solvent includes, for example, water, acetic acid, alcohols (e.g. methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g. hexane, cyclohexan, etc.), ethers (e.g. diethylene glycol dimethyl ether, dioxane, tetrahydrofuran, diethyl ether, etc.), esters (e.g. ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g. dimethylformamide, etc.), or a mixture of these solvents. The catalyst includes, for example, palladium, palladium-black, palladium-carbon, platinum, platinum oxide, copper chromite, Raney nickel, and the like. The catalyst is usually used in an amount of 0.02 mole to 1 mole to 1 mole of the starting compound. The reduction is usually carried out at about -20 to about 100°C, preferably at about 0 to about 70°C, under 1 to 10 pressures of hydrogen gas, for about 0.5 to about 20 hours.

In addition to the above reduction reaction, the reduction using a hydrogenating agent is preferably used. The hydrogenation agent includes, for example, lithium aluminum hydride, sodium borohydride, diborane, and the like. The hydrogenation agent is usually used at least in equimolar amount, preferably in an amount of 1 mole to 10 moles, to 1 mole of the compound (1c). This reduction reaction is usually carried out in an appropriate solvent such as water, lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), ethers (e.g. tetrahydrofuran, diethyl ether, diglyme, etc.), dimethylformamide, or a mixture of these solvents, at about -60 to 50°C, preferably at about -30°C to room temperature, for about 10 minutes to about 5 hours. When lithium aluminum hydride or diborane is used as a reducing agent, anhydrous solvent such as diethyl ether, tetrahydrofuran, diglyme, etc. is preferable.

[Reaction Scheme-4]



(1f) (1g)

[wherein R^1, R^2, R^3, R^5 and R^6 are the same as defined above, R^{7a} is a lower alkyl group or a lower alkenyl group, R^{15} and R^{16} are each hydrogen atom or a lower alkyl group, and X is a halogen atom]

The reaction between the compound (1f) and the compound (6) is usually carried out in an appropriate inert solvent in the presence or absence of a basic compound.

The inert solvent includes, for example, aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), ethers (e.g. tetrahydrofuran, dioxane, diethylen glycol dimethyl ether, etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride, tc.), lower alcohols (.g. m thanol, ethanol, isopropanol, butanol, tert-butanol, tc.), acetic-acid, ethyl ac tate, acetone, acetonitril, pyridine, dimethylsulfoxide, dimethylformamide, hexamethylphophoric acid triamide, or a mixture of these solvents. The basic compound includes, for example, metal carbonat s (e.g. sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, tc.), metal hydroxides (e.g. sodium hydroxide,

potassium hydroxid , tc.), sodium hydride, potassium, sodium, sodium amid , m tal alcoholates (e.g. sodium methylate, sodium ethylate, etc.), organic basic compounds (.g. pyridine, N-ethyldiisopropylamin , dimethylaminopyridine, tri thylamine, 1,5-diazabicyclo[4.3.0]nonen-5 (DBN), 1,8-diazabicyclo[5.4.0]-undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc.) and the like. The amount of the compound (1f) and the compound (6) is not critical, but the compound (6) is used at least in about equimolar amount, preferably in an amount of 1 mole to 10 moles, to 1 mole of the compound (1f). The reaction is usually carried out at about 0 to about 200 °C, preferably at about 0 to about 170 °C, for about 30 minutes to about 75 hours. An alkali metal halide (e.g. sodium iodide, potassium iodide, etc.) may be added to the reaction system.

The reaction between the compound (1f) and the compound (7) is carried out in an appropriate solvent or without solvent in the presence of a reducing agent. The solvent includes, for example, water, alcohols (e.g. methanol, ethanol, isopropanol, etc.), acetonitril, formic acid, acetic acid, ethers (e.g. dioxane, diethyl ether, diglyme, tetrahydrofuran, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), or a mixture of these solvents. The reducing agent includes, for example, formic acid, aliphatic acid alkali metal salts (e.g. sodium formate, etc.), hydrogenation agents (e.g. sodium borohydride, sodium cyano borohydride, lithium aluminum hydride, etc.), catalysts (e.g. palladium black, palladium-carbon, platinum oxide, platinum black, Raney nickel, etc.).

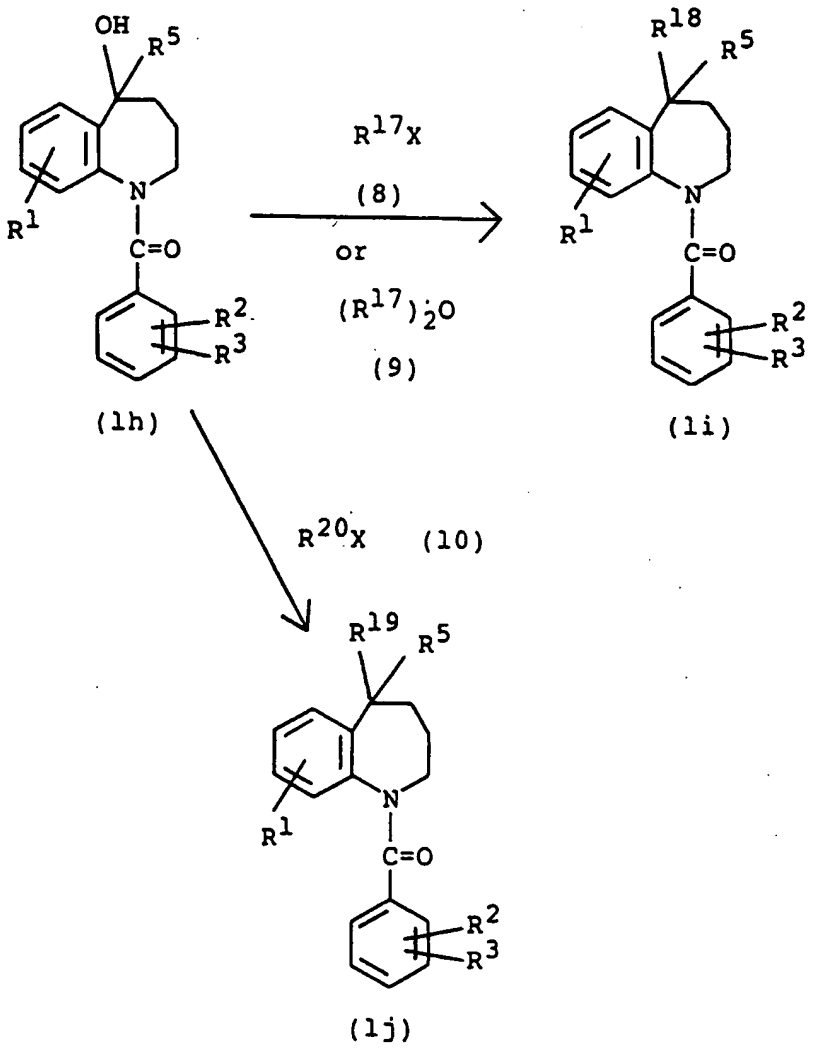
When formic acid is used as a reducing agent, the reaction is usually carried out at room temperature to about 200 °C, preferably at about 50 to about 150 °C, for about 1 to 10 hours. The formic acid is used in large excess amount to the amount of the compound (1f).

When a hydrogenation agent is used as a reducing agent, the reaction is usually carried out at about -30 to about 100 °C, preferably at about 0 to about 70 °C, for about 30 minutes to about 12 hours. The reducing agent is usually used in an amount of 1 mole to 20 moles, preferably in an amount of 1 mole to 6 moles, to 1 mole of the compound (1f). When lithium aluminum hydride is used as a reducing agent, ethers (e.g. diethyl ether, dioxane, tetrahydrofuran, diglyme, etc.) or aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.) is preferably used as a solvent.

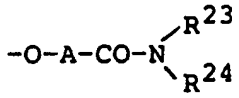
When a catalyst is used, the reaction is usually carried out under atmospheric pressure to 20 atms., preferably under atmospheric pressure to 10 atms of hydrogen gas, or in the presence of a hydrogen donor such as formic acid, ammonium formate, cyclohexene, hydrazine hydrate, etc. at about -30 to about 100 °C, preferably at about 0 to about 60 °C, for 1 to 12 hours. The catalyst is usually used in a ratio of 0.1 to 40 % by weight, preferably in a ratio of about 1 to about 20 % by weight, to the amount of the compound (1f).

The compound (7) is usually used at least in equimolar amount, preferably in an amount of 1 mole to large excess amount to 1 mole of the compound (1f).

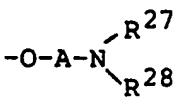
[Reaction Scheme-5]



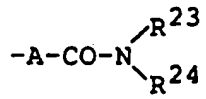
[wherein R^1, R^2, R^3, X and R^5 are the same as defined above, R^{18} is a lower alkanoyloxy group having a halogen substituent, or a lower alkoxy-substituted lower alkanoyloxy group, R^{19} is a lower alkenyloxy group, a group of the formula: -O-CO-A-NR^8R^9 (wherein A, R^8 and R^9 are the same as defined above), a group of the formula:



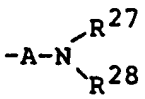
(wherein A, R^{23} and R^{24} are the same as defined above), a pyrrolidinylcarbonyl-lower alkoxy group having a lower alkoxycarbonyl on the pyrrolidine ring, a group of the formula:



(wherein A, R^{27} and R^{28} are the same as defined above), or a lower alkoxy group having a substituent selected from hydroxy group and a phenylsulfonyloxy group optionally being substituted by a lower alkyl group on the phenyl ring, R^{20} is a lower alkenyl group, a group of the formula: -CO-A-NR^8R^9 (wherein A, R^8, R^9 are the same as defined above), a group of the formula:



(wherein A, R^{23} and R^{24} are the same as defined above), a pyrrolidinylcarbonyl-lower alkyl group having a lower alkoxycarbonyl group on the pyrrolidine ring, a group of the formula:



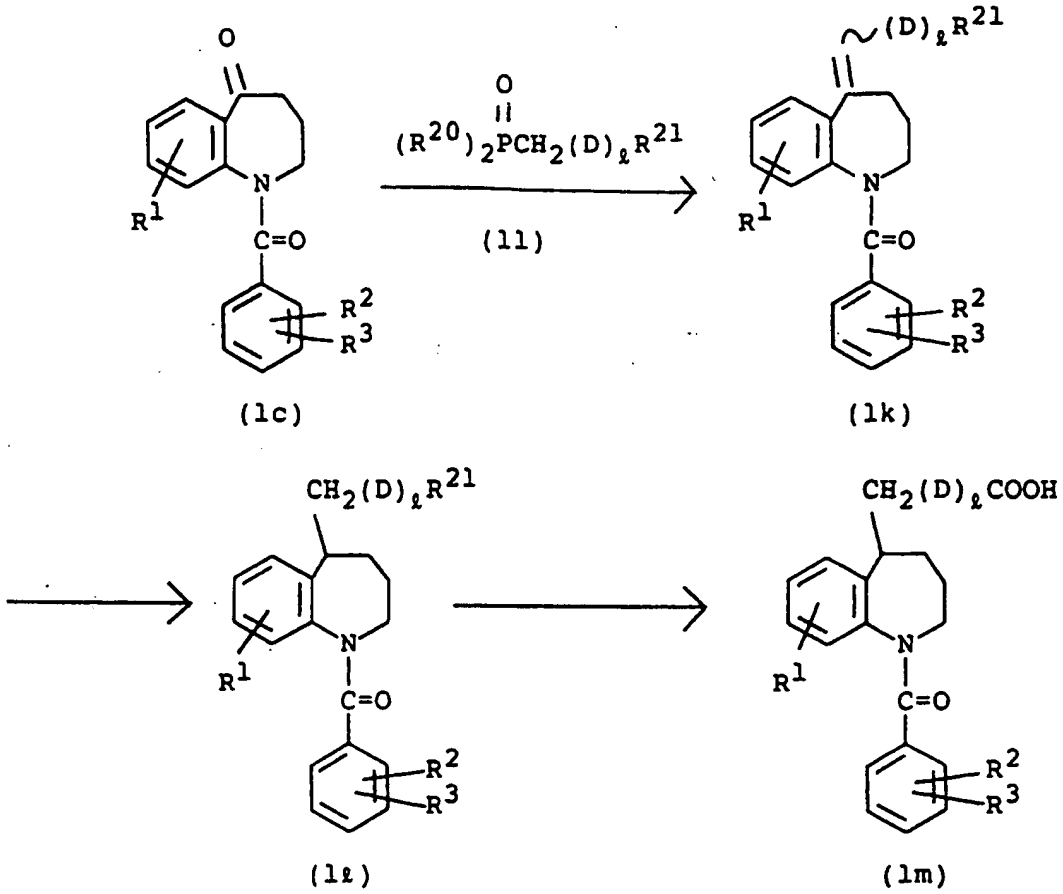
(wherein A, R^{27} and R^{28} are the same as defined above), or a lower alkyl group having a substituent selected from hydroxy group and a phenylsulfonyloxy group optionally being substituted by a lower alkyl group on the phenyl ring, R^{17} is a lower alkanoyl group having a halogen substituent, or a lower alkoxy-substituted lower alkanoyl group]

The reaction between the compound (1h) and the compound (8) or the compound (9) is carried out under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4.

The reaction between the compound (1h) and the compound (10) is carried out under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4.

When the compound (1i) is a compound of the formula (1i) wherein R^{18} is a lower alkanoyl group having a halogen substituent, the said compound (1i) can be reacted with a compound of the formula (11): HNR^8R^9 (wherein R^8 and R^9 are the same as defined above) under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4 to give the compound of the formula (1j) wherein R^{19} is a group of the formula: -O-CO-A-NR^8R^9 (wherein A, R^8 and R^9 are the same as defined above).

[Reaction Scheme-6]



[wherein R^1, R^2 and R^3 are the same as defined above, R^{20} is a lower alkoxy group, R^{21} is a lower alkoxycarbonyl group, cyano group or an amino group optionally being substituted by a lower alkyl group, D is a lower alkylene group and ℓ is an integer of 0 or 1]

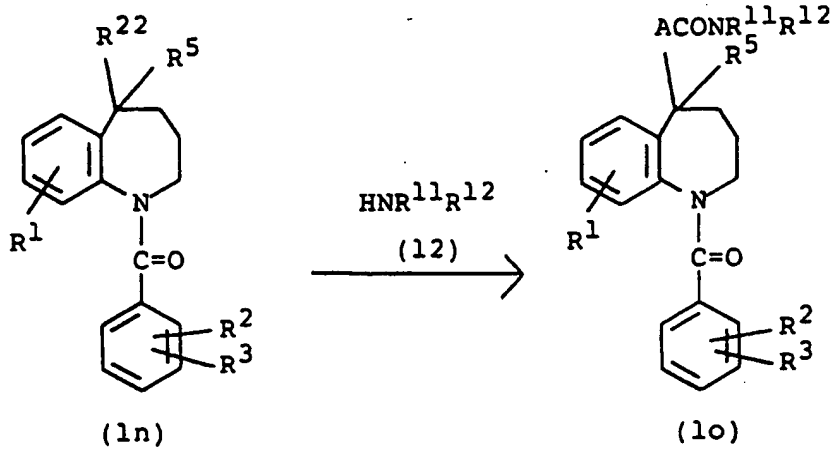
The reaction between the compound (1c) and the compound (11) is carried out in an appropriate solvent in the presence of a basic compound. The basic compound includes, for example, inorganic basic compounds (e.g. metal sodium, metal potassium, sodium hydride, sodium amide, sodium hydoxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc.), metal alcoholates (e.g. sodium methylate, sodium ethylate, potassium tert-butoxide, etc.), alkyl lithium, aryl lithium or lithium amide (e.g. methyl lithium, n-butyl lithium, phenyl lithium, lithium diisopropylamide, etc.), organic basic compounds (e.g. pyridine, piperidine, quinoline, triethylamine, N,N-dimethylaniline, etc.), and the like. The solvent may be any solvent which does not cause any trouble to the reaction, and includes, for example, ethers (e.g. diethyl ether, dioxane, tetrahydrofuran, monoglyme, diglyme, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), aliphatic hydrocarbons (e.g. n-hexane, heptane, cyclohexane, etc.), amines (e.g. pyridine, N,N-dimethylaniline, etc.), aprotic polar solvents (e.g. N,N-diemethylformamide, dimethylsulfoxide, hexamethylphosphoric acid triamide, etc.), alcohols (e.g. methanol, ethanol, isopropanol, etc.), and the like. The reaction is usually carried out at -80 to 150°C, preferably at about -80 to about 120°C, for about 0.5 to 15 hours.

The reaction of converting the compound (1k) into the compound (1ℓ) is carried out under the same reduction conditions as in the reaction of converting the compound (1c) into the compound (1e) in above mentioned Reaction Scheme-3. When a hydrogenation agent is used in said reduction reaction, the addition of methal halide (e.g. nickel chloride, etc.) into the reaction system advantageously promotes the reaction.

When the compound (1ℓ) is a compound of the formula (1ℓ) wherein R^{21} is a lower alkoxycarbonyl group, the reaction of converting the compound (1ℓ) into the compound (1m) is carried out in an appropriate solvent or without solvent in the presence of an acid or a basic compound. The solvent

includes, for xample, water, low r alcohols (.g. methanol, ethanol, isopropanol, tc.), ketons (e.g. acetone, methyl thylketone, etc.), ethers (.g. dioxane, tetra-hydrofuran, ethylene glycol dim thyl ether, etc.), fatty acids (e.g. acetic acid, formic acid, etc.), or a mixture of these solvents. The acid includes, for example, mineral acids (e.g. hydrochloric acid, sulfuric acid, hydrobromic acid, etc.), organic acids (e.g. formic acid, acetic acid, aromatic sulfonic acid, etc.), and the like. The basic compound includes, for example, metal carbonates (e.g. sodium carbonate, potassium carbonate, etc.), metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, etc.), and the like. The reaction is usually carried out at room temperature to about 200°C, preferably at room temperature to about 150°C, for about 10 minutes to about 25 hours.

[Reaction Scheme-7]

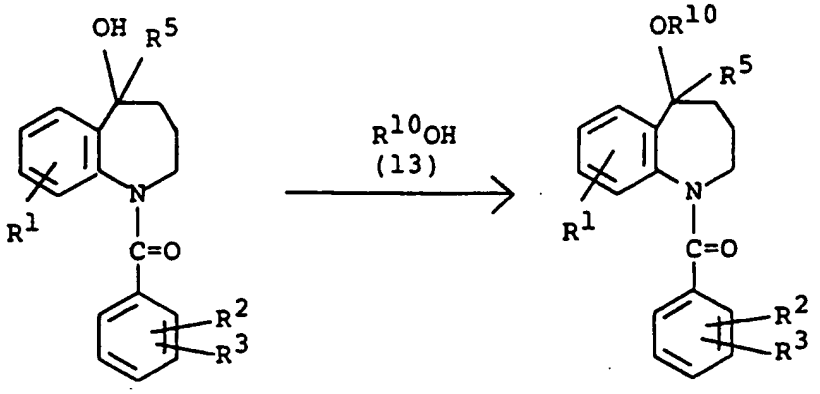


(1n) (1o)

[wherein R^1, R^2, R^3, R^5, R^{11}, R^{12} and A are the same as defined above, and R^{22} is a carboxy-substituted lower alkyl group]

The reaction between the compound (1n) and the compound (12) is carried out under the same conditions as in the reaction between the compound (2) and the compound (3) in above mentioned Reaction Scheme-1.

[Reaction Scheme-8]



(1p) (1q)

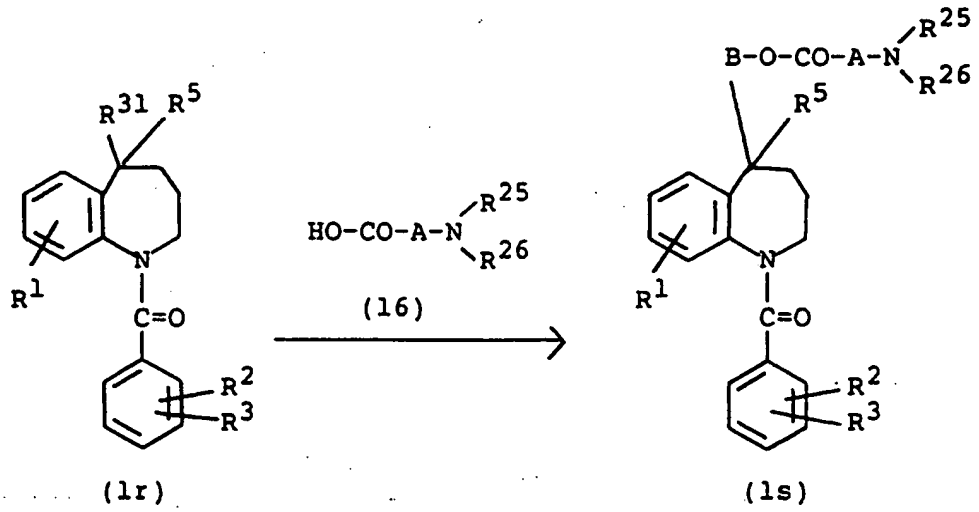
[wherein R^1, R^2, R^3, R^5 and R^{10} are the same as defined above]

The reaction between the compound (1p) and the compound (13) is carried out in an appropriate solvent in the presence of a basic compound. To th reaction system, it may be preferabl to add a

condensing agent such as dicyclohexylcarbodiimide, carbonyldiimidazol , 1- thyl-3-(3'-dimethylaminopropyl)carbodiimid , and th like. Th basic compound and th solv nt us d ther in are the same as those for the reaction b tween the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4. The compound (13) is used at least in equimolar amount, preferably in an amount of 1 mole to 2 moles, to 1 mole of the compound (1p). The reaction is usually carried out at 0 to 100°C, preferably at about 0 to about 70°C, for about 1 to about 15 hours.

Alternatively, the reaction may proceed as follows. That is, before reacting with the compound (1p), the amino acid residue for R^{10} of the compound (13) may be protected by a conventional protecting group for amino acid such as phenyl-lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, etc.) and lower alkoxycarbonyl groups (e.g. tert-butoxycarbonyl, etc.), which is removed thereafter by a conventional deprotecting reaction such as catalytic reduction, hydrolysis, and the like, and further the resultant may be converted into the compound (1q).

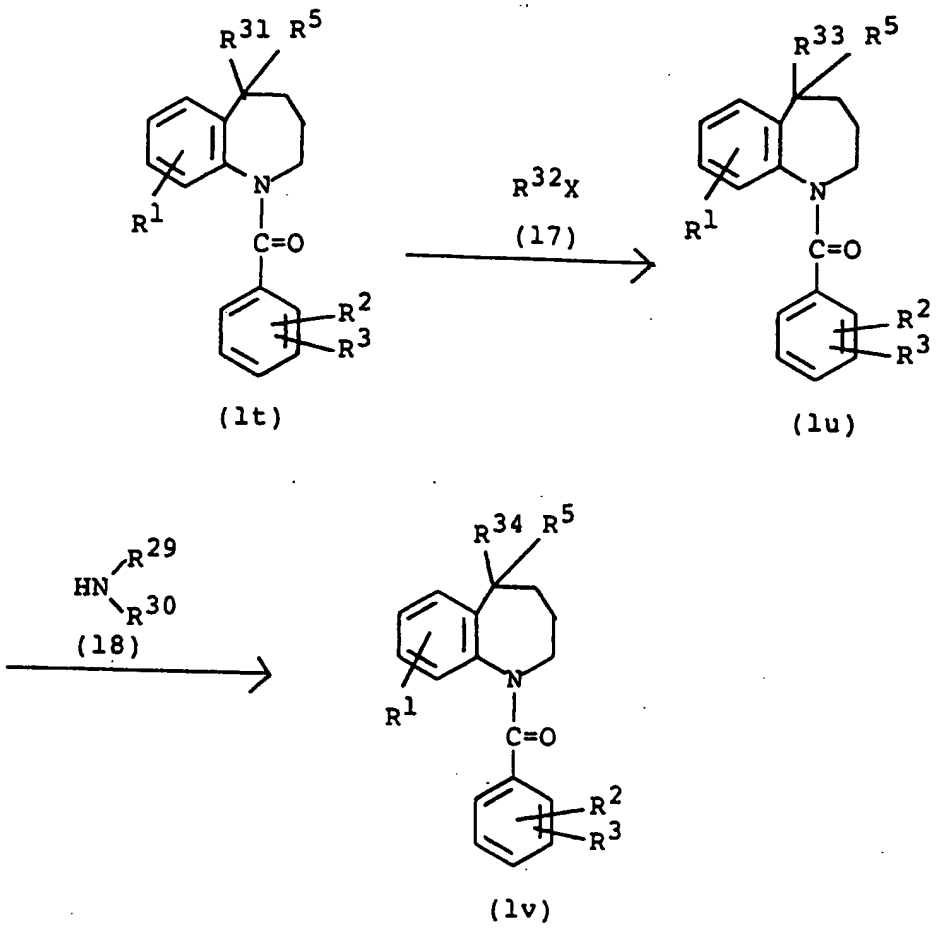
[Reaction Scheme-9]



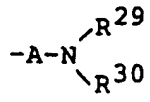
[wherein R^1, R^2, R^3, R^5, R^{25}, R^{26}, A and B are the same as defined above, and R^{31} is hydroxy-substituted lower alkyl group]

The reaction between the compound (1r) and the compound (16) is carried out under the same conditions as in the reaction between the compound (1p) and the compound (13) in above mentioned Reaction Scheme-8.

[Reaction Scheme-10]



[wherein R^1, R^2, R^3, R^5, R^{29}, R^{30}, R^{31} and X are the same as defined above, R^{32} is a phenylsulfonyl group optionally having a lower alkyl substituent on the phenyl ring, R^{33} is a phenylsulfonyloxy-substituted lower alkyl group optionally having a lower alkyl substituent on the phenyl ring,
R^{34} is a group of the formula:

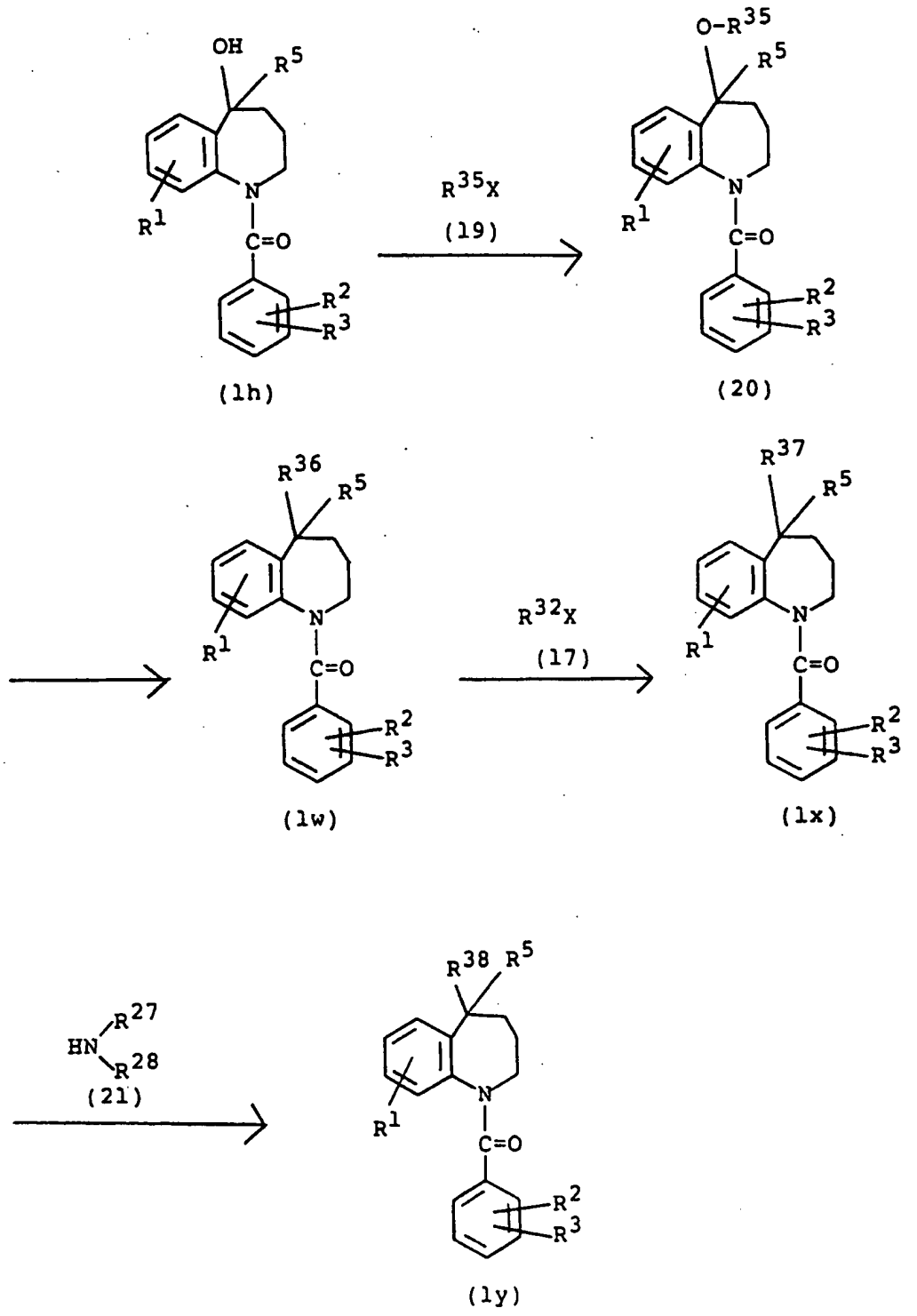


(wherein A, R^{29} and R^{30} are the same as defined above)]

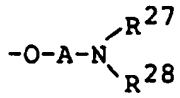
The reaction between the compound (1t) and the compound (17) is carried out under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4.

The reaction between the compound (1u) and the compound (18) is carried out under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4.

[Reaction Scheme-11]



[wh rein R^1, R^2, R^3, R^5, R^{27}, R^{28} and R^{32} are th same as defined above, R^{36} is a low r alkoxy group substituted by hydroxy group, R^{37} is a low r alkoxy group which is substitut d by a phenylsulfonyloxy group optionally being substituted by a lower alkyl group on the phenyl ring, and R^{38} is a group of the formula:



(wherein R^{27}, R^{28} and A are the same asdefined above)]

The reaction between the compound (1h) and the compound (19) is carried out under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4.

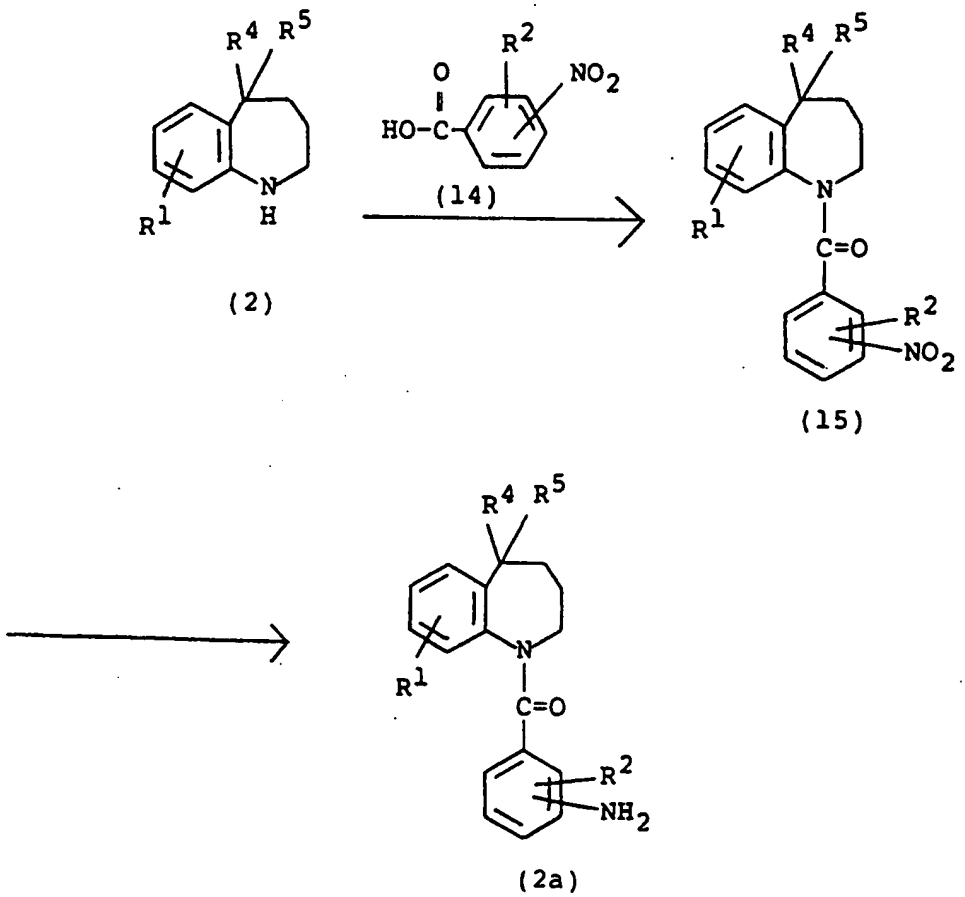
The reaction of converting the compound (20) into the compound (1w) is carried out under the same conditions as in the reduction reaction of the compound (1c) into the compound (1d) in above mentioned Reaction Scheme-3.

The reaction between the compound (1w) and the compound (17) is carried out under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4.

The reaction between the compound (1x) and the compound (21) is carried out under the same conditions as in the reaction between the compound (1f) and the compound (6) in above mentioned Reaction Scheme-4.

The starting compound (2a) may be prepared by the following processes.

[Reaction Scheme-12]



[wherein R^1, R^2, R^4 and R^5 are th same as defined abov]

The reaction between the compound (2) and the compound (14) is carried out under the same conditions as in the reaction between the compound (2) and the compound (3) in above mention d Reaction Scheme-1.

The reaction of converting the compound (15) to the compound (2a) is carried out by
(A) reduction reaction using a catalyst in an appropriate solvent; or
(B) reduction reaction using a combination of metal or metal salt and an acid, or a combination of metal or metal salt and an alkali metal hydroxide, sulfite or ammonium salt, and the like, as a reducing agent in an inert solvent.

When the process (A) is employed, the solvent includes, for example, water, acetic acid, alcohols (e.g. methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g. hexane, cyclohexane, etc.), ethers (e.g. dioxane, tetrahydrofuran, diethyl ether, diethylene glycol dimethyl ether, etc.), esters (e.g. ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, etc.), or a mixture of these solvents. The catalyst includes, for example, palladium, palladium-black, palladium-carbon, platinum, platinum oxide, copper chromite, Raney nickel, and the like. The catalyst is usually used in an amount of about 0.02 to about 1 mole, to 1 mole of the starting compound. The reaction is usually carried out at about -20 to about 150°C, preferably at about 0 to about 100°C, under 1 to 10 pressures of hydrogen gas, for about 0.5 to about 10 hours. An acid such as hydrochloric acid, etc. may be added to the reaction system.

When the process (B) is employed, there is used as a reducing agent a combination of iron, zinc, tin or stannous chloride and a mineral acid (e.g. hydrochloric acid, sulfuric acid, etc.), or a combination of iron, iron sulfate, zinc or tin and an alkali metal hydroxide (e.g. sodium hydroxide, etc.), a sulfide (e.g. ammonium sulfide, etc.) or an ammonium salt (e.g. aqueous ammonia, ammonium chloride, etc.). The inert solvent includes, for example, water, acetic acid, methanol, ethanol, dioxane, and the like. The conditions for the above reduction reaction are chosen according to the kinds of the reducing agent used therein, for example, when stannous chloride and hydrochloric acid are used, the reaction advantageously proceeds at about 0°C to room temperature for about 0.5 to 10 hours. The reducing agent is used at least in equimolar amount, usually in an amount of 1 mole to 5 moles, to 1 mole of the staring compound.

The compound (1) wherein R^1 is hydroxy group can be obtained by dealkylation of the compound (1) wherein R^1 is a lower alkoxy group. The said dealkylation reaction is carried out by heat-treatment in a mixture of an acid (e.g. hydrobromic acid, hydrochloric acid, etc.) and a solvent (e.g. water, methanol, ethanol, isopropyl alcohol, etc.) at 30 to 150°C, preferably at 50 to 120°C, or by hydrolysis. The hydrolysis is carried out in an appropriate solvent in the presence of an acid. The solvent includes, for example, water, lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), ethers (e.g. dioxane, tetrahydrofuran, etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride, etc.), polar solvents (e.g. acetonitrile, etc.), or a mixture of these solvents. The acid includes, for example, mineral acids (e.g. hydrochloric acid, sulfuric acid, hydrobromic acid, etc.), Lewis acids (e.g. boron trifluoride, aluminum chloride, boron tribromide, etc.), iodides (e.g. sodium iodide, potassium iodide, etc.), a mixture of a iodide and a Lewis acid, and the like. The reaction is usually carried out at room temperature to 150°C, preferably at room temperature to 100°C, for about 0.5 to about 15 hours.

Among the active compounds (1) of the present invention, the compounds having an acidic group can easily be converted into salts by treating with a pharmaceutically acceptable basic compound. The basic compound includes, for example, metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, etc., alkali metal carbonates or hydrogen carbonates such as sodium carbonate, sodium hydrogen carbonate, etc., alkali metal alcoholates such as sodium methylate, potassium ethylate, etc. Besides, among the active compounds (1) of the present invention, the compounds having a basic group can be easily converted into acid addition salts thereof by treating with a pharmaceutically acceptable acid. The acid includes, for example, inorgainc acids such as sulfuric acid, nitric acid, hydrochloric acid, hydrobromic acid, etc., and organic acids such as acetic acid, p-toluenesulfonic acid, ethanesulfonic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, benzoic acid, etc. These salts are also useful as an active ingredient as like as the compounds (1) in the free form.

In addition, the compounds (1) of the present invention include stereoisomers and optical isomers, and these isomers are also useful as an active ingredient in this invention.

The compounds of the present invention thus obtained can easily be isolated from the reaction system and purified by conventional methods. The isolation and purification methods are, for example, distillation method, recrystallization method, column chromatography, ion exchange chromatography, gel chromatography, affinity chromatography, preparative thin layer chromatography, extraction with a solvent, and the like.

The active compounds (1) and their salts of the present invention are useful as a vasopressin antagonist

and are used in the form of a conventional pharmaceutical preparation. The preparation is prepared by using conventional diluents or carriers such as fillers, thickening agents, binders, wetting agents, disintegrators, surfactants, lubricants, and the like. The pharmaceutical preparations may be selected from various forms in accordance with the desired utilities, and the representative forms are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (e.g. solutions, suspensions, etc.), and the like. In order to form in tablets, there are used carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starches, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g. dry starch, sodium arginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white sugar, stearin, cacao butter, hydrogenated oils, etc.), absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (e.g. starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc.), and the like. Moreover, the tablets may also be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film coated tablets, or double or multiple layer tablets. In the preparation of pills, the carriers include vehibles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin, talc, etc.), binders (e.g. gum arabic powder, tragacanth powder, gelatin, ethanol, etc.), disintergrators (e.g. laminaran, agar, etc.), and the like. In the preparation of suppositories, the carriers include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, and the like. Capsules can be prepared by charging a mixture of the compound of the present invention and the above carriers into hard gelatin capsules or soft capsules in a usual manner. In the preparation of injections, the solutions, emulsions or suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents, such as water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents, and the like. Besides, the pharmaceutical preparations may optionally be incorporated with coloring agents, preservatives, perfumes, flavors, sweeting agents, and other medicines, if required.

The amount of the active compound of the present invention (active ingredient) to be incorporated into the anti-vasopressin preparations is not specified but may be selected from a broad range, but usually, it is preferably in the range of about 1 to about 70 % by weight, more preferably about 5 to about 50 % by weight.

The anti-vasopressin preparation of the present invention may be administered in any method, and suitable method for administration may be determined in accordance with various forms of preparation, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For instance, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. The injections are intraveneously administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if required. Suppositories are administered intrarectal route.

The dosage of the anti-vasopressin agent of the present invention may be selected in accordance with the usage, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but is usually in the range of about 0.6 to 50 mg of the active compound of the present invention per 1 kg of body weight of the patient per day. The active compound is preferably contained in an amount of about 10 to 1000 mg per the dosage unit.

Examples

The present invention is illustrated by the following Preparations of anti-vasopressin agent, Reference Examples of processes for preparing the starting compounds to be used for preparing the active compounds, Examples of processes for preparing the active compounds, and Experiments of the activities of the active compounds of the present invention.

Preparation 1

Film coated tablets are prepared from the following components.

Components	Amount
7-Hydroxy-5-methylamino-1-[4-(2-chlorobenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine	150 g
Avicel (tradename; Asahi Chemical Industry Co, Ltd.)	40 g
Corn starch	30 g
Magnesium stearate	2 g
Hydroxypropyl methylcellulose	10 g
Polyethylene glycol-6000	3 g
Castor oil	40 g
Ethanol	40 g

The active compound of the present invention, Avicel, corn starch and magnesium stearate are mixed and kneaded and the mixture is tabletted using a conventional pounder (R 10 mm) for sugar coating. The tablets thus obtained are coated with a film coating agent consisting of hydroxypropyl methylcellulose, polyethylene glycol-6000, castor oil and ethanol to give film coated tablets.

Preparation 2

Tablets are prepared from the following components.

Components	Amount
5-Dimethylamino-1-[4-(4-carbamoylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine	150 g
Citric acid	1.0 g
Lactose	33.5 g
Dicalcium phosphate	70.0 g
Pullonic F-68	30.0 g
Sodium laurylsulfate	15.0 g
Polyvinylpyrrolidone	15.0 g
Polyethylene glycol (Carbowax 1500)	4.5 g
Polyethylene glycol (Carbowax 6000)	45.0 g
Corn starch	30.0 g
Dry sodium stearate	3.0 g
Dry magnesium stearate	3.0 g
Ethanol	q.s.

The active compound of the present invention, citric acid, lactose, dicalcium phosphate, Pullonic F-68 and sodium laurylsulfate are mixed. The mixture is screened with No. 60 screen and is granulated with an alcohol solution containing polyvinylpyrrolidone, carbowax 1500 and 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-like mass. Corn starch is added to the mixture and the mixture is continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and put into a tray and then dried in an oven at 100°C for 12 to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixture is tabletted to form the desired shape.

The core tablets thus prepared are vanished and dusted with talc in order to guard from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are vanished several times. In order to give round shape and smooth surface to the tablets, further undercoating and coating with lubricant are applied thereto. The tablets are further coated with a coloring coating material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gloss.

Preparation 3

An injection preparation is prepared from the following components.

Components	Amount
5-Dimethylamino-1-{4-[2-(3-methylphenyl)acetylamino]benzoyl}-2,3,4,5-t tr-ahydro-1H-benzazepine	5 g
Polyethylene glycol (molecular weight: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methyl-paraben	0.18 g
Propyl-paraben	0.02 g
Distilled water for injection	10.0 ml

The above parabens, sodium metabisulfite and sodium chloride are dissolved in distilled water of half volume of the above with stirring at 80°C. The solution thus obtained is cooled to 40°C, and the active compound of the present invention and further polyethylene glycol and polyoxyethylene sorbitan monooleate are dissolved in the above solution. To the solution is added distilled water for injection to adjust to the desired volume, and the solution is sterilized by filtering with an appropriate filter paper to give an injection preparation.

Reference Example 1

To a solution of 5-dimethylamino-2,3,4,5-tetrahydro-1H-benzazepine (50 g) in a mixture of acetone (400 ml) and water (200 ml) is added potassium carbonate (38.8 g), and thereto is added p-nitrobenzoyl chloride (40 g) with stirring under ice-cooling, and the mixture is stirred at room temperature overnight. To the reaction mixture is added an appropriate amount of water, and the precipitated crystals are collected by filtration and dried to give 5-dimethylamino-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine (71 g) as pale yellow powder, mp. 139 - 142°C.

Reference Example 2

In ethanol (500 ml) is dispersed 10 % Pd-C (5 g), and thereto is added 5-dimethylamino-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine (64.1 g), and the mixture is subjected to catalytic reduction at ordinary room temperature under atmospheric pressure. After reduction, 10 % Pd-C is removed by filtration, and the filtrate is concentrated under reduced pressure to give 5-dimethylamino-1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine (56.1 g) as white powder, mp. 120 - 122°C.

Reference Example 3

5-Hydroxy-7-chloro-1-[2-methoxy-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.7 g), dimethylaminopyridine (0.83 g) and dimethylaminopyridine hydrochloride (0.72 g) are dissolved in chloroform (15 ml), and thereto are added N-tert-butoxycarbonyl-L-methionine (0.56 g) and dicyclohexylcarbodiimide (0.93 g), and the mixture is stirred at room temperature for 3 hours. To the mixture are added methanol (3 ml) and acetic acid (0.7 ml), and the mixture is stirred at room temperature for 30 minutes. The insoluble materials are removed by filtration, and to the filtrate is added 5 % aqueous sodium hydrogen sulfate solution, and the mixture is extracted with dichloromethane. The dichloromethane layer is washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over magnesium sulfate. The solvent is evaporated and the resulting residue is purified by silica gel column chromatography (eluent; dichloromethane : methanol = 150 : 1) to give 5-(N-tert-butoxycarbonyl-L-methionyloxy)-7-chloro-1-[2-methoxy-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.27 g).

^{1}H-NMR ($CDCl_3$) δ ; 1.29 - 2.92, 3.35 - 5.40, 6.09 - 6.35 (total 30H, m, 1.45 (s), 1.47 (s)), 6.61 - 8.00 (12H, m)

Using the appropriate starting compounds, the following compounds are obtained in the same manner as in Reference Example 3.

5-(N-tert-Butoxycarbonyl-L-alanyloxy)-1-[2-chloro-4-(2-m thylb nzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine

^{1}H-NMR ($CDCl_3$) δ ; 0.95 - 3.05, 3.29 - 5.22, 5.95 - 6.27 (total 23H, m), 6.86 - 8.17 (13H, m)

5-(N-tert-Butoxycarbonylglycyloxy)-1-[2-chloro-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-

benzaz pine

^{1}H-NMR ($CDCl_3$) δ ; 1.30 - 3.09, 3.69 - 5.29, 5.91 - 6.35 (total 21H, m), 6.77 - 8.48 (13H, m)

5-(N-tert-Butoxycarbonyl-L-methionyloxy)-1-[2-chloro-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine

^{1}H-NMR ($CDCl_3$) δ ; 1.05 - 3.06, 3.25 - 3.63, 4.01 - 5.37 (total 26H, m), 5.97 - 6.28 (1H, m), 6.72 - 8.72 (13H, m)

Reference Example 4

Using the appropriate starting compounds, the following compounds are obtained in the same manner as in Reference Example 1.

5-(3-Hydroxypropoxy)-7-chloro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.4 - 2.6 (7H, m), 2.7 - 3.0 (1H, m), 3.0 - 4.1 (7H, m), 4.3 - 5.1 (2H, m), 6.6 - 7.0 (2H, m), 7.1 - 8.0 (4H, m)

5-[3-(p-Toluenesulfonyloxy)propoxy]-7-chloro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.35 - 2.65 (9H, m), 2.65 - 3.0 (1H, m), 3.05 - 3.95 (5H, m), 3.95 - 4.45 (2H, m), 4.5 - 5.05 (2H, m), 6.6 - 7.05 (2H, m), 7.1 - 8.05 (8H, m)

5-(2-Hydroxyethoxy)-7-chloro-1-(2-methoxy-A-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.35 - 2.6 (4H, m), 2.7 - 3.0 (1H, m), 3.0 - 4.1 (7H, m), 4.35 - 5.0 (2H, m), 6.6 - 7.0 (2H, m), 7.1 - 8.05 (5H, m)

5-[2-(p-Toluenesulfonyloxy)ethoxy]-7-chloro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.35 - 2.6 (7H, m), 2.65 - 2.95 (1H, m), 3.0 - 3.95 (5H, m), 4.1 - 5.05 (4H, m), 6.55 - 7.05 (2H, m), 7.05 - 7.6 (4H, m), 7.65 - 8.0 (4H, m)

5-Methoxycarbonylmethyl-7-chloro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.2 - 1.5 (1H, m), 1.5 - 2.3 (3H, m), 2.6 - 2.95 (2H, m), 2.95 - 3.25 (1H, m), 3.3 - 4.2 (7H, m), 4.45 - 5.15 (1H, m), 6.65 - 6.85 (1H, m), 6.85 - 7.0 (1H, m), 7.02 (1H, d, J = 1.8 Hz), 7.1 - 8.05 (3H, m)

5-Methoxycarbonylmethyl-7-chloro-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow prisms

^{1}H-NMR ($CDCl_3$) δ ; 1.2 - 1.75 (2H, m), 1.75 - 2.3 (2H, m), 2.6 - 3.15 (1H, m), 3.15 - 3.4 (1H, m), 3.76 (3H, s), 4.05 - 5.2 (2H, m), 6.54 (1H, d, J = 8.3 Hz), 6.92 (1H, dd, J = 8.3 Hz, 2.2 Hz), 7.1 - 7.25 (1H, m), 7.52 (2H, d, J = 8.8 Hz), 8.06 (2H, dd, J = 8.8 Hz, 2 Hz)

5-[2-(p-Toluenesulfonyloxy)ethyl]-7-chloro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.0 - 1.4 (1H, m), 1.4 - 2.15 (4H, m), 2.15 - 2.4 (1H, m), 2.4 - 2.55 (3H, m), 2.9 - 3.3 (2H, m), 3.35 - 4.5 (6H, m), 6.6 - 8.0 (10H, m)

5-Cyanomethyl-7-chloro-1-(3-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

^{1}H-NMR ($CDCl_3$) δ ; 1.38 - 2.37, 2.66 - 4.22, 4.41 - 4.68, 5.03 - 5.24 [total 12H, m, (3.79(s))], 6.55 - 8.00 [6H, m, (6.76 (dd, J = 1.6 Hz, 8.3 Hz)), (6.92 (d, J = 1.4 Hz)), (7.23 (d, J = 2.0 Hz))]

5-Ethoxycarbonylmethyl-7-chloro-1-(3-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

^{1}H-NMR ($CDCl_3$) δ ; 1.25 - 2.26, 2.61 - 4.66, 5.01 - 5.25 [total 17H, m, (1.28 (3H, t, J = 7.1 Hz)), (3.83 (3H, s))], 6.57 (1H, d, J = 9.5 Hz), 6.85 - 7.31 (4H, m), 7.63 (1H, d, J = 8.3 Hz)

N-{[7-Fluoro-1-(2-chloro-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepins-5-yl]oxym thylcarbonyl}-L-alanine methyl ester

Yellow oil

^{1}H-NMR ($CDCl_3$) δ ; 1.37 - 1.53 (3H, m), 1.54 - 4.25 (8H, m), 4.40 - 5.05 (3H, m), 6.65 - 8.35 (7H, m)

N-{[7-Fluoro-1-(2-chloro-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepin-5-yl]oxymethylcarbonyl}-L-proline methyl ester

Yellow oil

^{1}H-NMR ($CDCl_3$) δ ; 1.37 - 4.19 (16H, m), 4.23 - 5.07 (3H, m), 6.56 - 8.43 (6H, m)

5-Methoxycarbonylmethyl-7-chloro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow powder

^{1}H-NHR ($CDCl_3$) δ; 1.50 - 2.31 (4H, m), 2.45 - 5.20 (5H, m), 2.57, 2.61 (3H, each s), 3.75 (3H, s), 6.55 (1H, d, J=8.4 Hz), 6.89 (1H, dd, J=2.3 Hz, 8.4 Hz), 7.09 (1H, d, J=2.3 Hz), 7.16 (1H, d, J=8.4 Hz), 7.78 (1H,dd, J=2.2 Hz, 8.4 Hz), 8.00 (1H, d, J=2.2 Hz)

5-Methoxycarbonylmethyl-7-chloro-1-(2-chloro-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow powder

mp. 133 - 134 °C

^{1}H-NHR ($CDCl_3$) δ ; 1.05 - 2.28 (4H, m), 2.57 - 3.05 (2H, m), 3.06 - 3.32 (1H, m), 3.33 - 3.85 (1H, m), 3.74 (3H, s), 4.39 - 4.67 (1H, m), 6.78 - 7.19 (3H, m), 7.38 (1H, d, J=8.2 Hz), 7.93 (1H, dd, J=8.2 Hz, 2.1 Hz), 8.17 (1H, d, J=2.1 Hz)

5-Methoxycarbonylmethyl-7-chloro-1-(3-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Slightly yellow powder

mp. 139.5 - 141 °C

^{1}H-NHR ($CDCl_3$) δ ; 1.16 - 2.31 (4H, m), 2.61 - 3.09 (2H, m), 3.12 - 3.40 (1H, m), 3.41 - 5.23 (2H, m), 3.72 (3H, s), 3.83 (3H, s), 6.58 (1H, d, J=8.3 Hz), 6.85 - 7.24 (4H, m), 7.63 (1H, d, J=8.3 Hz)

5-[2-(p-Toluenesulfonyloxy)ethoxy]-7-chloro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.12 - 5.14 (17H, m), 6.50 (1H, dd, J=16Hz, 8.4 Hz), 6.91 (1H, d, J=8.4 Hz), 7.10 - 8.45 (8H, m)

5-[3-(p-Toluenesulfonyloxy)propoxy]-7-chloro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Slightly yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.09 - 3.08 (13H, m), 3.09 - 5.18 (6H, m), 6.50 (1H, dd, J=17.8 Hz, 8.4 Hz), 6.84 - 8.42 (9H, m)

5-(2-Methoxyacetyloxy)-7-chloro-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.7 - 3.2 (5H, m), 3.36, 3.46 (total 3H, s), 4.10, 4.29 (total 2H, s), 4.7 - 5.2 (1H, m), 6.1 - 6.2 (1H, m), 6.57 (1H, d, J=8.3 Hz), 6.9 - 7.1 (1H, m), 7.2 - 7.5 (1H, m), 7.5 - 7.6 (2H, m), 8.0 - 8.2 (2H, m)

5-Methoxycarbonylmethyl-7-fluoro-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow oil

^{1}H-NHR ($CDCl_3$) δ ; 1.22 - 1.70 (2H, m), 1.77 - 2.23 (2H, m), 2.65 - 3.04 (2H, m), 3.12 - 3.30 (1H, m), 3.75 (3H, s), 4.07 - 4.35 (1H, m), 4.40 - 5.18 (1H, m), 6.44 - 6.70 (2H, m) , 6.80 - 7.05 (1H, m), 7.40 - 7.60 (2H, m), 7.95 - 8.10 (2H, m), 8.15 - 8.28 (1H, m)

5-Hydroxy-7-fluoro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.52 - 2.36 (4H, m), 2.68 - 2.95 (1H, m), 3.12 (1H, brs), 3.44 - 4.03 (3H, m), 4.65 - 5.17 (2H, m), 6.50 - 6.76 (2H, m), 6.80 - 8.03 (4H, m)

5-(3-Morpholinopropoxy)-7-fluoro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.43 - 2.62 (11H, m), 2.53, 2.59 (3H, s), 2.72 - 3.03 (1H, m), 3.10 - 3.83 (7H, m), 4.36 - 5.07 (2H, m), 6.46 - 6.71 (2H, m), 6.86 - 8.20 (4H, m)

5-[3-(1-Imidazolyl)propoxy]-7-fluoro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow oil

^{1}H-NHR ($CDCl_3$) δ ; 1.37 - 2.63 (6H, m), 2.52, 2.59, 2.60 (total 3H, s), 2.73 - 3.05 (1H, m), 3.10 - 3.80 (2H, m), 3.96 - 5.07 (4H, m), 6.46 - 6.72 (2H, m), 6.85 - 7.20 (4H, m), 7.26 - 8.23 (3H, m)

5-Methoxycarbonylmethyl-7-fluoro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.19 - 2.26 (4H, m), 2.57 - 2.90 (2H, m), 2.95 - 3.20 (1H, m), 3.35 - 4.27 (4H, m), 3.75 (3H, s), 4.48 - 5.12 (1H, m), 6.52 - 6.67 (1H, m), 6.71 - 8.02 (5H, m)

5-[2-(p-Toluenesulfonyloxy)ethoxy]-7-fluoro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow oil

^{1}H-NHR ($CDCl_3$) δ ; 1.34 - 1.88 (2H, m), 1.95 - 2.38 (2H, m), 2.40, 2.43, 2.45 (total 3H, s), 2.70 - 2.91

(1H, m), 3.43 - 4.00 (5H, m), 4.13 - 4.47 (2H, m), 4.56 - 5.03 (2H, m), 6.54 - 7.96 (10H, m)

5-(3-Hydroxypropoxy)-7-fluoro-1-(2-m thyl-4-nitrob nzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.38 - 2.67 (8H, m), 2.53, 2.59 (total 3H, s), 2.72 - 3.08 (1H, m), 3.14 - 3.93 (5H, m), 4.25 - 5.11 (2H, m), 6.47 - 6.73 (2H, m), 6.86 - 8.18 (4H, m)

5-[3-(p-Toluenesulfonyloxy)propoxy]-7-fluoro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.38 - 2.63 (6H, m), 2.42, 2.44 (total 3H, s), 2.52, 2.57, 2.58 (total 3H, s), 2.73 - 3.03 (1H, m), 3.10 - 3.83 (2H, m), 4.05 - 5.03 (4H, m), 6.45 - 6.70 (2H, m), 6.86 - 8.19 (8H, m)

5-[3-(1-Pyrrolidinyl)propoxy]--7-fluoro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine hydroiodide

Pale yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.40 - 1.90 (2H, m), 1.95 - 2.63 (7H, m), 2.53, 2.58, 2.59 (total 3H, s), 2.75 - 3.90 (10H, m), 4.42 - 4.98 (2H, m), 5.22 (1H, brs), 6.47 - 6.68 (2H, m), 6.92 - 7.38 (2H, m), 7.56 - 8.32 (2H, m)

5-(2-Hydroxyethoxy)-7-fluoro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow oil

^{1}H-NHR ($CDCl_3$) δ ; 1.38 - 2.63 (5H, m), 2.53, 2.58, 2.59 (total 3H, s), 2.76 - 3.93 (4H, m), 4.40 - 5.00 (2H, m), 6.49 - 8.18 (6H, m)

5-Hydroxy-7-fluoro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow powder

^{1}H-NHR (DMSO-d_6) δ ; 1.40 - 2.31 (4H, m), 2.49, 2.54, 2.55 (total 3H, s), 2.62 - 3.43 (1H, m), 4.55 - 5.06 (2H, m), 5.77 (1H, brs), 6.66 - 6.98 (2H, m), 7.10 - 7.50 (2H, m), 7.60 - 8.36 (2H, m)

5-Hydroxymethyl-7-fluoro-1-(2-methoxy-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NHR ($CDCl_3$) δ; 1.13 - 1.40 (1H, m), 1.46 - 2.31 (3H, m), 2.40 - 3.50 (2H, m), 2.66 (1H, brs), 3.55 - 4.13 (5H, m), 4.53 - 5.03 (1H, m), 6.57 (1H, dt, J = 8.5 Hz, 2.8 Hz), 6.67 - 7.18 (2H, m), 7.28 - 8.03 (3H, m)

5-(2-Hydroxyethyl)-7-chloro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.38 - 2.35 (7H, m), 2.36 - 4.00 (7H, m), 4.30 - 4.53 (1H, m), 6.57 (1H, d, J = 8.3 Hz), 6.89 (1H, dd, J = 2.2 Hz, 8.3 Hz), 7.03 (1H, d, J = 8.3 Hz), 7.13 (1H, d, J = 2.2 Hz), 7.67 - 7.82 (1H, m), 7.91 - 8.08 (1H, m)

5-[2-(p-Toluenesulfonyloxy)ethyl]-7-chloro-1-(2-methyl-4-nitrobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

^{1}H-NHR ($CDCl_3$) δ ; 1.07 - 2.78 (13H, m (2.46 s)), 2.79 - 3.38 (2H, m), 3.97 - 4.48 (2H, m), 6.56 (1H, d, J = 8.2 Hz), 6.90 (1H, dd, J = 2.2 Hz, 8.2 Hz), 6.93 (1H, d, J = 8.4 Hz), 7.02 (1H, d, J = 2.2 Hz), 7.20 - 7.64 (2H, m), 7.72 - 7.91 (3H, m), 7.98 (1H, d, J = 2.1 Hz)

Reference Example 5

Using the appropriate starting compounds, the following compounds are obtained in the same manner as in Reference Example 2.

5-[3-(p-Toluenesulfonyloxy)propoxy]-7-chloro-1-(2-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pink amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.3 - 2.35 (6H, m), 2.44 (3H, s), 2.55 - 4.0 (8H, m), 4.25 (2H, t, J = 6 Hz), 4.5 - 5.15 (2H, m), 5.93 (1H, s), 6.1 - 6.45 (1H, m), 6.66 (1H, d, J = 8.4 Hz), 6.88 (1H, dd, J = 8.4 Hz, 2.4 Hz), 6.99 (1H, d, J = 8 Hz), 7.29 (1H, S), 7.35 (2H, d, J = 8.2 Hz), 7.81 (2H, d, J = 8.3 Hz)

5-[2-(p-Toluenesulfonyloxy)ethoxy]-7-chloro-1-(2-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.3 - 2.35 (4H, m), 2.45 (3H, s), 2.65 - 2.95 (1H, m), 3.05 - 4.0 (7H, m), 4.0 - 5.1 (4H, m), 5.90 (1H, brs), 6.05 - 6.4 (1H, m), 6.64 (1H, d, J = 8.3 Hz), 6.75 - 7.15 (2H, m), 7.15 - 7.55 (3H, m), 7.83 (2H, d, J = 8.2 Hz)

5-Methoxycarbonylmethyl-7-chloro-1-(2-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzaz pine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.15 - 2.3 (4H, m), 2.55 - 3.25 (3H, m), 3.3 - 4.05 (9H, m), 4.1 - 4.7 (1H, m), 5.85 -

6.45 (2H, m), 6.65 - 6.8 (1H, m), 6.8 - 7.4 (3H, m)

5-M thoxycarbonylmethyl-7-chloro-1-(4-aminobenzoyl)-2,3,4,5-t trahydro-1H-b nzaz pine

Colorless prisms (recrystalliz d from ethanol)

^{1}H-NMR ($CDCl_3$) δ ; 1.15 - 2.3 (4H, m), 2.5 - 3.05 (2H, m), 3.05 - 3.3 (1H,m), 3.3 - 4.3 (6H, m), 4.35 - 5.3 (1H, m), 6.43 (2H, d, J = 8.5 Hz), 6.61 (1H, d, J = 8.4 Hz), 6.85 - 7.0 (1H, m), 7.0 - 7.4 (3H, m)

5-[2-(p-Toluenesulfonyloxy)ethyl]-7-chloro-1-(2-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.0 - 2.4 (6H, m), 2.46 (3H, s), 2.5 - 4.4 (10H, m), 5.85 - 7.25 (6H, m), 7.3 - 7.5 (2H, m), 7.65 - 7.9 (2H, m)

5-Cyanomethyl-7-chloro-1-(3-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

^{1}H-NMR ($CDCl_3$) δ ; 1.21 - 2.33, 2.40 - 4.70, 5.05 - 5.39 (total 14H, m), 6.38 - 7.42 (4H, m), 6.43 (1H, d, J = 8.1 Hz), 7.04 (1H, dd, J = 2.3 Hz, 8.4 Hz)

5-Ethoxycarbonylmethyl-7-chloro-1-(3-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.11 - 2.28 [7H, m, (1,27 (t, J = 7.1 Hz))], 2.49 - 4.61, 5.01 - 5.35 (total 12H, 3.68 (s)-), 6.40 (1H, d, J = 8.0 Hz), 6.49 - 7.44 (4H, m), 6.95 (1H, dd, J = 2.3 Hz, 8.3 Hz)

5-Methoxycarbonylmethyl-7-chloro-1-(2-methyl-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

^{1}H-NHR ($CDCl_3$) δ ; 0.83 - 2.47 (4H, m), 2.37 (3H, s), 2.48 - 5.25 (7H, m), 3.72 (3H, s), 6.16 (1H, d, J = 8.3 Hz), 6.41 (1H, s), 6.54 (1H, d, J = 8.3 Hz), 6.64 (1H, d, J = 8.2 Hz), 6.90 (1H, d, J = 8.2 Hz), 7.00 - 7.42 (1H, m)

N-{[7-Fluoro-1-(2-chloro-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepin-5-yl]oxymethylcarbonyl}-L-alanine methyl ester

Slightly yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.35 - 1.51 (3H, m), 1.51 - 5.14 (15H, m), 6.10 - 7.42 (7H, m)

N-{[7-Fluoro-1-(2-chloro-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepin-5-yl]oxymethylcarbonyl}-L-proline methyl ester

Slightly yellow amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.33 - 2.64 (8H, m), 2.64 - 3.00 (1H, m), 3.01 - 4.44 (9H, m), 4.45 - 5.13 (3H, m), 6.12 - 7.46 (6H, m)

5-Methoxycarbonylmethyl-7-chloro-1-(2-chloro-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow amorphous

^{1}H-NHR ($CDCl_3$) ; 1.09 - 2.36 (4H, m), 2.45 - 5.19 (7H, m), 3.71 (3H, s), 6.12 - 7.50 (2H, m), 6.27 (1H, dd, J = 2.1 Hz, 8.3 Hz), 6.54 (1H, d, J = 2.1 Hz), 6.92 (1H, d, J = 2.1 Hz), 7.05 (1H, dd, J = 2.1 Hz, 6.1 Hz)

5-Methoxycarbonylmethyl-7-chloro-1-(3-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Slightly yellow amorhpous

^{1}H-NHR ($CDCl_3$) δ ; 1.01 - 2.29 (4H, m), 2.44 - 3.31 (3H, m), 3.32 - 5.29 (4H, m), 3.68, 3.71 (each 3H, s), 6.41 (1H, d, J = 8.0 Hz), 6.50 - 6.78 (2H, m), 6.79 - 6.91 (1H, m), 6.95 (1H, d, J = 8.4 Hz), 7.04 - 7.24 (1H, m)

5-[2-(p-Toluenesulfonyloxy)ethoxy]-7-chloro-1-(2-methyl-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.01 - 2.52 (4H, m), 2.32 (3H, s), 2.43 (3H, s), 3.53 - 4.78 (9H, m), 5.86 - 8.03 (10H, m)

5-[3-(p-Toluenesulfonyoxy)propoxy]-7-chloro-1-(2-methyl-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Slightly yellow amorphous

^{1}H-NHR ($CDCl_3$) δ ; 1.13 - 3.03 (7H, m), 2.33 - 2.43 (6H, each s), 3.04 - 5.18 (8H, m), 5.98 - 8.07 (10H, m)

5-(2-Methoxyacetyloxy)-7-chloro-1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

mp. 166 - 169 °C

(recrystallized from dichloromethane/diethyl ether) 5-Methoxycarbonylmethyl-7-fluoro-1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepin

Pale yellow oil

^{1}H-NHR ($CDCl_3$) δ ; 1.06 - 2.20 (4H, m), 2.40 - 3.22 (3H, m), 3.26 - 4.28 (3H, m), 3.71 (3H, s), 4.35 - 5.30 (1H, m), 6.23 - 6.45 (2H, m), 6.53 - 6.72 (2H, m), 6.75 - 7.20 (3H, m)

5-(3-Morpholinopropoxy)-7-fluoro-1-(2-m thyl-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-b nzazepin
Pale yellow amorphous
^{1}H-NHR ($CDCl_3$) δ ; 1.41 - 2.63 (10H, m), 2.33 (3H, s), 2.75 - 3.00 (1H, m), 3.32 - 3.92 (8H, m), 4.27 - 5.16 (2H, m), 5.98 - 6.75 (4H, m), 6.80 - 7.38 (2H, m)

5-[2-(p-Toluenesulfonyloxy)ethoxy]-7-fluoro-1-(2-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine
Pale yellow oil
^{1}H-NHR ($CDCl_3$) δ ; 1.29 - 2.30 (4H, m), 2.45 (3H, s), 2.62 - 2.88 (1H, m), 2.96 - 3.97 (4H, m), 3.46 (3H, s), 4.08 - 4.43 (2H, m), 4.52 - 5.07 (2H, m), 5.86 - 6.00 (1H, m), 6.06 - 6.38 (1H, m), 6.47 - 6.75 (2H, m), 6.90 - 7.40 (2H, m), 7.36 (2H, d, J = 8.2 Hz), 7.82 (2H, d, J = 8.2 Hz)

5-[3-(1-Pyrrolidinyl)propoxy]-7-fluoro-1-(2-methyl-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine
Pale yellow amorphous
^{1}H-NHR ($CDCl_3$) δ ; 1.40 - 2.70 (16H, m), 2.33 (3H, s), 2.73 - 2.96 (1H, m), 3.30 - 3.86 (4H, m), 4.28 - 5.14 (2H, m), 6.00 - 6.25 (1H, m), 6.30 - 6.72 (4H, m), 6.75 - 7.35 (1H, m)

5-[2-(1,3-Dioxo-1,2,3,4,5,6,7-octahydroisoindol-2-yl)ethoxy]-7-fluorol-1-(2-methyl-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine
Colorless oil
^{1}H-NHR ($CDCl_3$) δ ; 1.30 - 2.47 (13H, m), 2.33 (3H, s), 2.66 - 4.01 (8H, m), 4.32 - 5.13 (2H, m), 6.04 - 6.26 (4H, m), 6.80 - 7.36 (2H, m)

5-Methoxycarbonylmethyl-7-fluoro-1-(2-methoxy-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine
Pale yellow amorphous
^{1}H-NHR ($CDCl_3$) δ ; 1.41 - 2.15 (4H, m), 2.57 - 3.14 (3H, m), 3.35 - 4.31 (3H, m), 3.59 (3H, s), 3.74 (3H, s), 4.45 - 5.15 (IH, m), 5.88 - 6.17 (2H, m), 6.51 - 7.07 (4H, m)

5-[2-(p-Toluenesulfonyloxy)ethyl]-7-chloro-1-(2-methyl-4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine
Yellow amorphous
^{1}H-NHR ($CDCl_3$) δ ; 1.10 - 2.53 (13H, m (2.31, 2.45 each 3H, each s)), 2.54 - 4.46 (6H, m), 5.95 - 6.70 (3H, m), 6.71 - 7.56 (5H, m (7.36, 2H, d, J = 8.1 Hz)), 7.80 (2H, d, J = 8.1 Hz)

Example 1

To a solution of 5-dimethylamino-2,3,4,5-tetrahydro-1H-benzazepine (50 g) in a mixture of acetone (400 ml) and water (200 ml) is added potassium carbonate (38.8 g), and thereto is added A-[2-(2-chlorophenyl)-acetylamino]benzoyl chloride (66.5 g) with stirring under ice-cooling, and the mixture is stirred at room temperature overnight. Water is added to the reaction mixture, and the mixture is extracted with dichloromethane. The extract is dried over magnesium sulfate, and the solvent is distilled off under reduced pressure. The resulting residue is purified by silica gel column chromatography, and recrystallized from methanol to give 5-dimethyl-1-{4-[2-(2-chlorophenyl)acetylamino]benzoyl}-2,3,4,5-tetrahydro-1H-benzazepine (99.3 g) as white powder, mp. 187 - 189 °C.

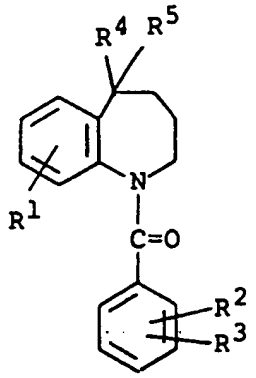
Example 2

To 2-chlorophenylacetic acid (0.44 g) is added thionyl chloride (15 ml), and the mixture is stirred at room temperature for 2 hours. Thionyl chloride is distilled off, and the resultant is further distilled off by subjecting twice to azeotrophy with toluene. The resulting residue is dissolved in dichloromethane (10 ml). Separately, to a solution of 5-dimethylamino-1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-benzazepine (0.40 g) in dichloromethane is added triethylamine (0.36 ml) under ice-cooling, and thereto is added dropwise the above obtained 2-(2-chlorophenyl)acetyl chloride solution. After addition, the mixture is stirred at room temperature for one hour, washed twice with water, dried over magnesium sulfate, and concentrated. The resulting residue is purified by silica gel column chromatography (eluent; chloroform : methanol = 200 : 1), and recrystallized from methanol/diethyl ether to give 5-dimethylamino-1-{4-[2-(2-chlorophenyl)-acetylamino]benzoyl}-2,3,4,5-tetrahydro-1H-benzazepine (0.29 g) as white powder, up. 187 - 189 °C.

Examples 3 to 85

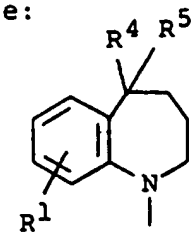
Using the appropriate starting compounds, the following compounds of Table 1 are obtained in the same manner as in Examples 1 and 2.

Table 1

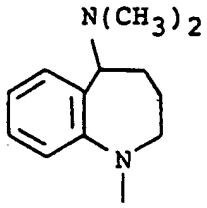


Example 3

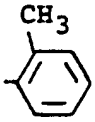
Structure:



:



R^2: H

R^3: 4-NHCOCH$_2$- 

Crystalline form: White powder

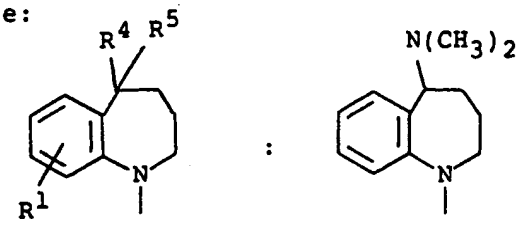
Recrystallization solvent: Methanol/diethyl ether

Melting point: 153 - 154.5°C

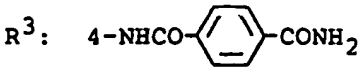
Form: Free

Example 4

Structure:



R^2: H



Crystalline form: White powder

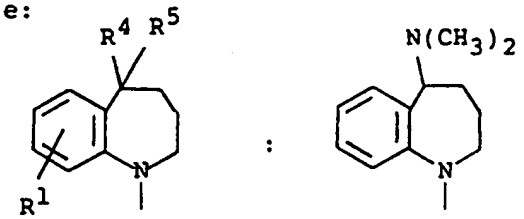
Recrystallization solvent: Diethyl ether

Melting point: 226 - 231°C

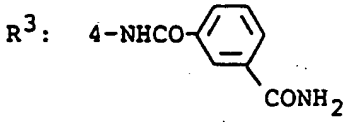
Form: Free

Example 5

Structure:



R^2: H



Crystalline form: White powder

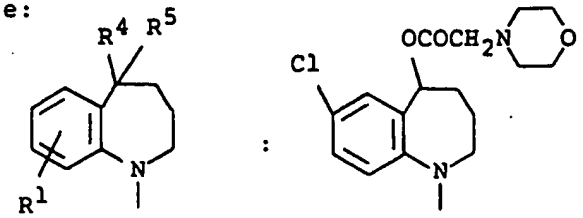
Recrystallization solvent: Ethanol/n-hexane

Melting point: 224 - 229°C

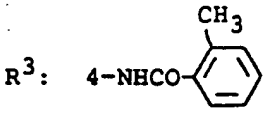
Form: Free

Example 6

Structure:



R^2: 2-OCH_3



R^3: 4-NHCO-

Crystalline form: White powder

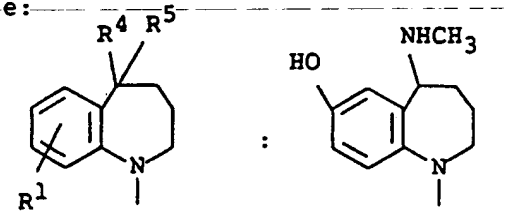
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 179 - 181°C

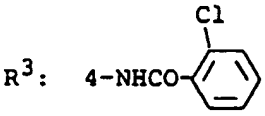
Form: Hydrochloride

Example 7

Structure:



R^2: 2-Cl



R^3: 4-NHCO-

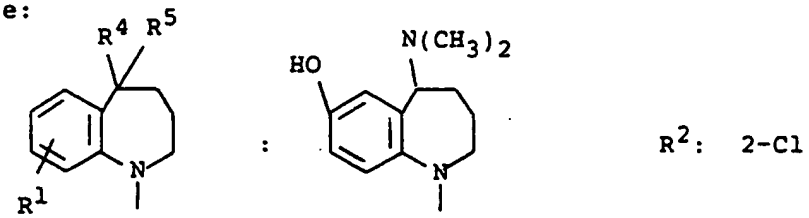
Crystalline form: Colorless amorphous

Form: Free

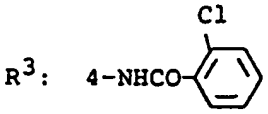
NMR analysis: 1)

Example 8

Structure:



R^2: 2-Cl



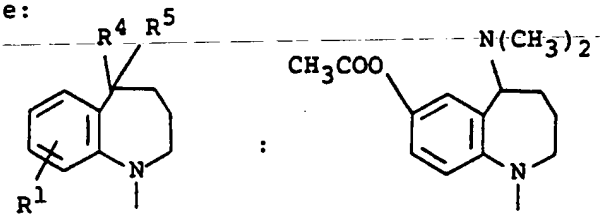
Crystalline form: Colorless amorphous

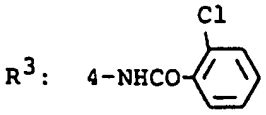
Form: Free

NMR analysis: 2)

Example 9

Structure:





R^2: 2-Cl

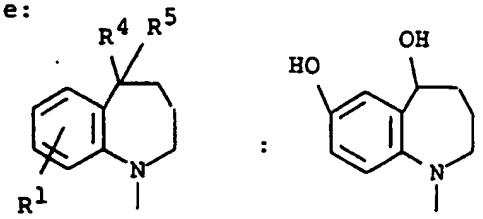
Crystalline form: Colorless amorphous

Form: Free

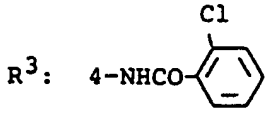
NMR analysis: 3)

Example 10

Structure:



R^2: 2-Cl



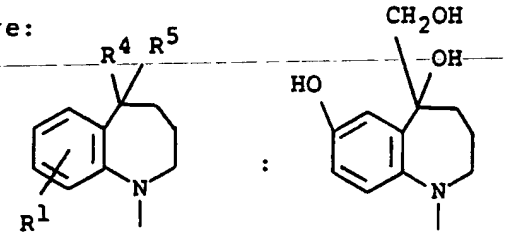
Crystalline form: Colorless amorphous

Form: Free

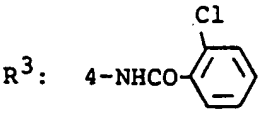
NMR analysis: 4)

Example 11

Structure:



R^2: 2-Cl



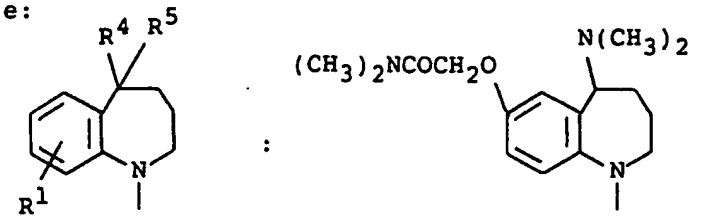
Crystalline form: Colorless amorphous

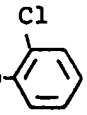
Form: Free

NMR analysis: 5)

Example 12

Structure:



R^3: 4-NHCO- 

R^2: 2-Cl

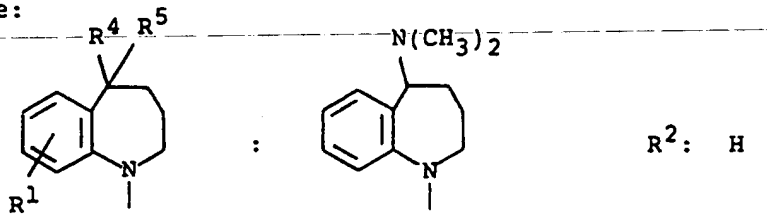
Crystalline form: Colorless amorphous

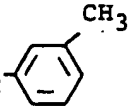
Form: Free

NMR analysis: 6)

Example 13

Structure:



R^3: 4-NHCOCH$_2$- 

R^2: H

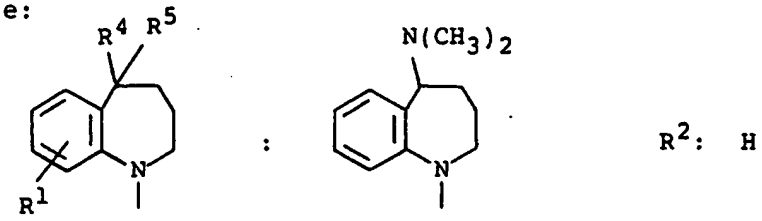
Crystalline form: Colorless amorphous

Form: Free

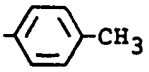
NMR analysis: 7)

Example 14

Structure:



R^2: H

R^3: 4-$NHCOCH_2$-  -CH_3

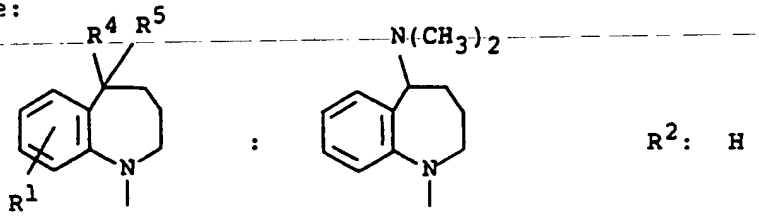
Crystalline form: Colorless amorphous

Form: Free

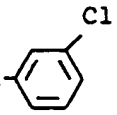
NMR analysis: 8)

Example 15

Structure:



R^2: H

R^3: 4-$NHCOCH_2$- 

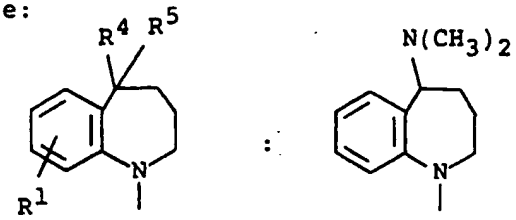
Crystalline form: Colorless amorphous

Form: Free

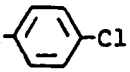
NMR analysis: 9)

Example 16

Structure:



R^2: H

R^3: 4-$NHCOCH_2$-  -Cl

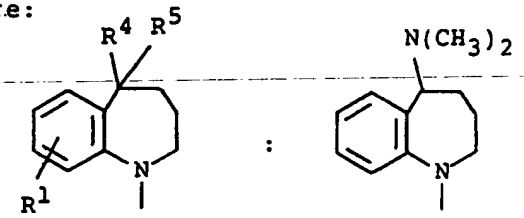
Crystalline form: Colorless amorphous

Form: Free

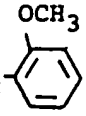
NMR analysis: 10)

Example 17

Structure:



R^2: H

R^3: 4-$NHCOCH_2$- 

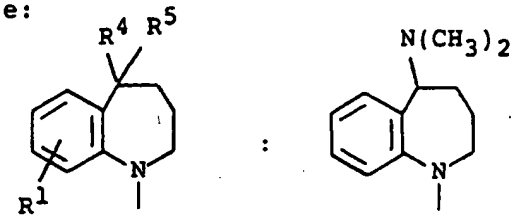
Crystalline form: Colorless amorphous

Form: Free

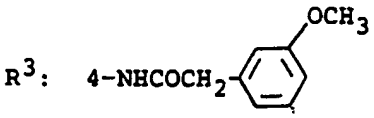
NMR analysis: 11)

Example 18

Structure:



R^2: H



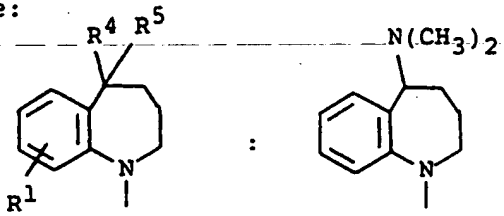
Crystalline form: Colorless amorphous

Form: Free

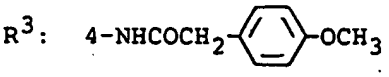
NMR analysis: 12)

Example 19

Structure:



R^2: H



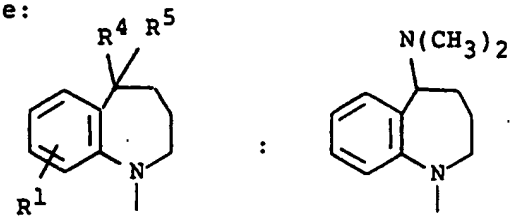
Crystalline form: Colorless amorphous

Form: Free

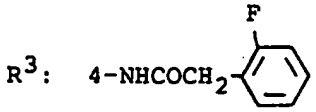
NMR analysis: 13)

Example 20

Structure:



R^2: H



Crystalline form: White powder

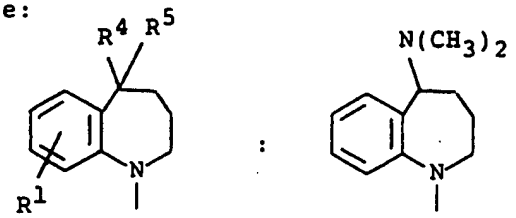
Recrystallization solvent: Methanol/diethyl ether

Melting point: 189.5 - 191°C

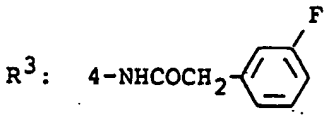
Form: Free

Example 21

Structure:



R^2: H



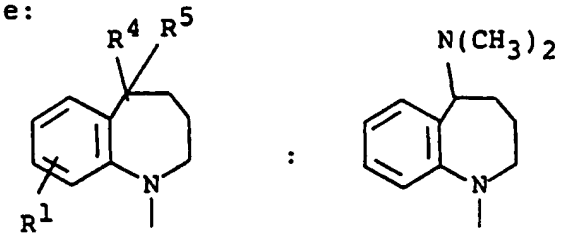
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 14)

Example 22

Structure:



R^2: H

R^3: 4-NHCOCH$_2$-(4-F-phenyl)

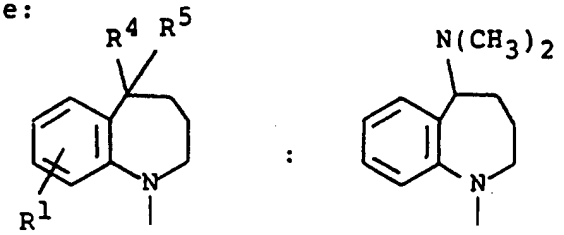
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 15)

Example 23

Structure:



R^2: H

R^3: 4-NHCOCH$_2$-(2,3-dimethoxyphenyl)

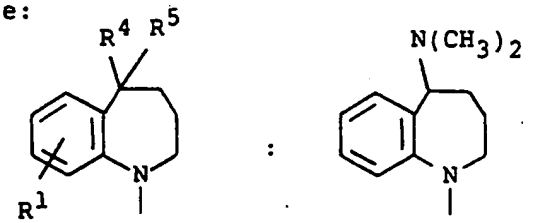
Crystalline form: Colorless amorphous

Form: Free

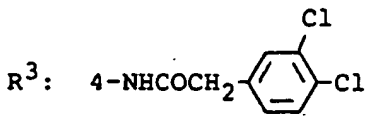
NMR analysis: 16)

Example 24

Structure:



R^2: H



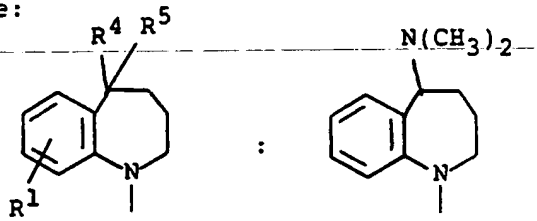
Crystalline form: Colorless amorphous

Form: Free

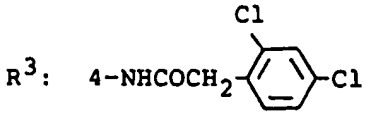
NMR analysis: 17)

Example 25

Structure:



R^2: H



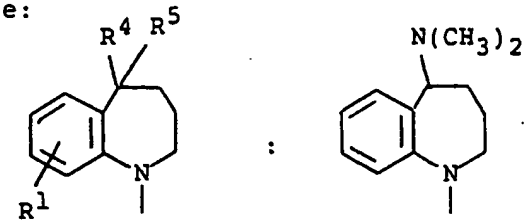
Crystalline form: Colorless amorphous

Form: Free

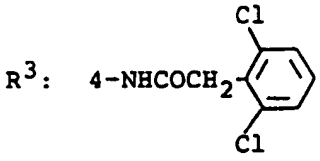
NMR analysis: 18)

Example 26

Structure:



R^2: H



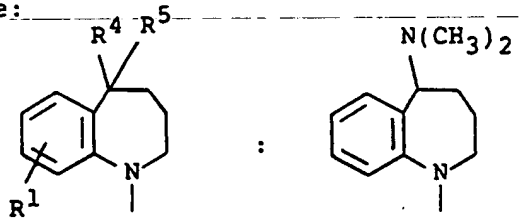
Crystalline form: Colorless amorphous

Form: Free

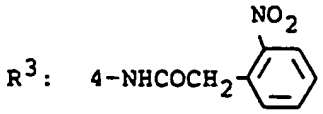
NMR analysis: 19)

Example 27

Structure:



R^2: H



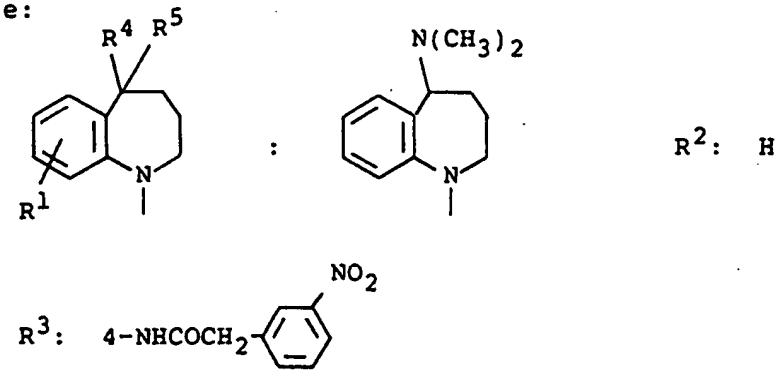
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 20)

Example 28

Structure:



R^2: H

R^3: 4-$NHCOCH_2$-(2-NO_2-phenyl)

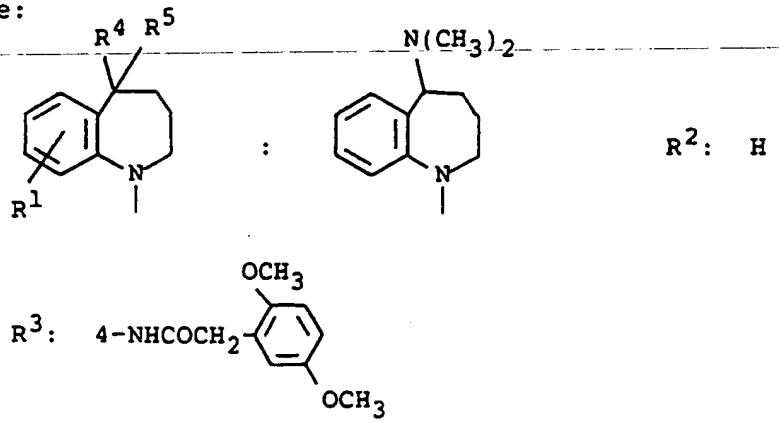
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 21)

Example 29

Structure:



R^2: H

R^3: 4-$NHCOCH_2$-(2,5-di-OCH_3-phenyl)

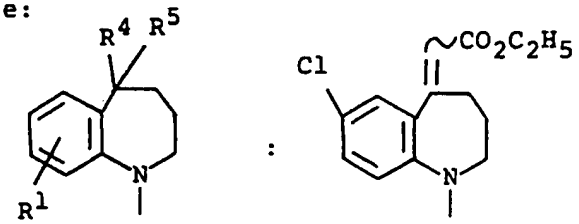
Crystalline form: Colorless amorphous

Form: Free

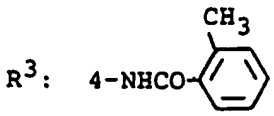
NMR analysis: 22)

Example 30

Structure:



R^2: 2-CH_3



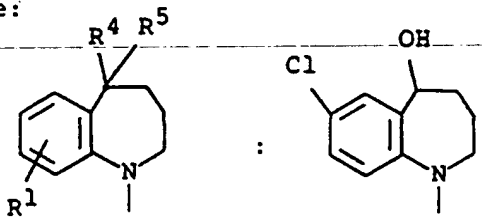
Crystalline form: Colorless amorphous

Form: Free

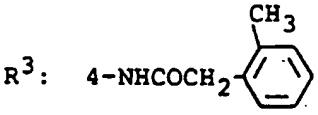
NMR analysis: 23)

Example 31

Structure:



R^2: 2-Cl



Crystalline form: White powder

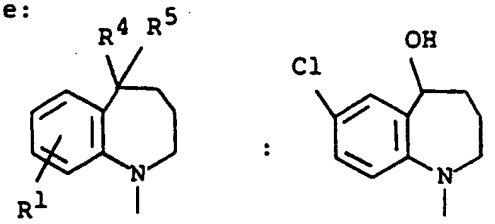
Recrystallization solvent: Methanol/diethyl ether

Melting point: 192.5 - 194.5°C

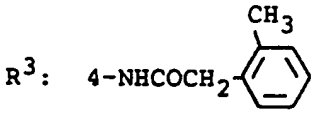
Form: Free

Example 32

Structure:



R^2: 2-F



Crystalline form: White powder

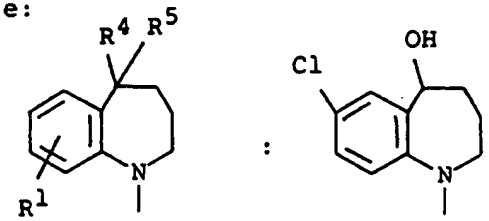
Recrystallization solvent: Methanol/diethyl ether

Melting point: 210 - 211°C

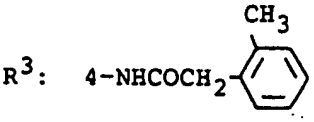
Form: Free

Example 33

Structure:



R^2: 2-CH_3



Crystalline form: White powder

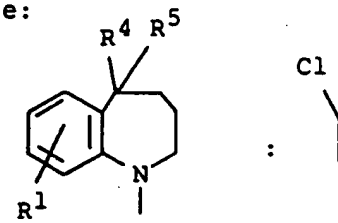
Recrystallization solvent: Methanol/diethyl ether

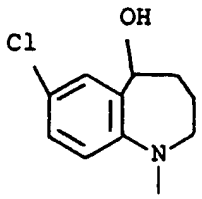
Melting point: 221 - 222°C

Form: Free

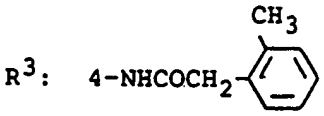
Example 34

Structure:



: 

R^2: $2\text{-}OCH_3$



R^3: $4\text{-}NHCOCH_2$

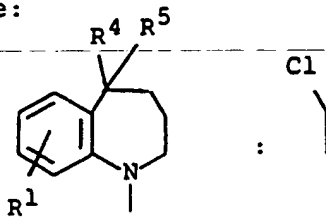
Crystalline form: Colorless amorphous

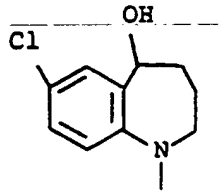
Form: Free

NMR analysis: 24)

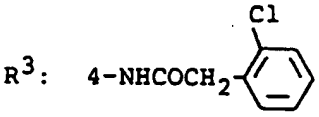
Example 35

Structure:



: 

R^2: 2-F



R^3: $4\text{-}NHCOCH_2$

Crystalline form: White powder

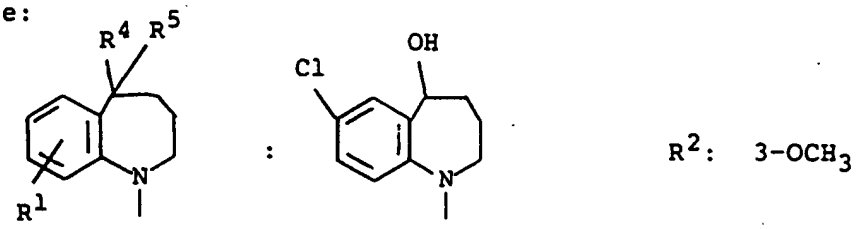
Recrystallization solvent: Methanol/diethyl ether

Melting point: 175 - 176°C

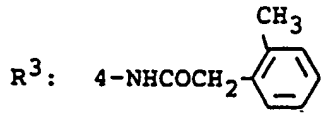
Form: Free

Example 36

Structure:



R^2: 3-OCH_3



Crystalline form: White powder

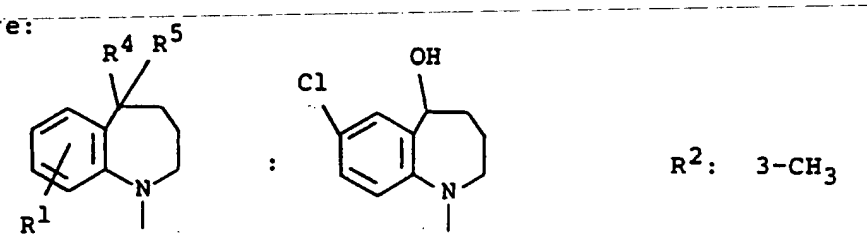
Recrystallization solvent: Methanol/diethyl ether

Melting point: 212 - 215°C

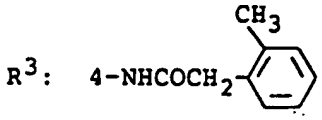
Form: Free

Example 37

Structure:



R^2: 3-CH_3



Crystalline form: White powder

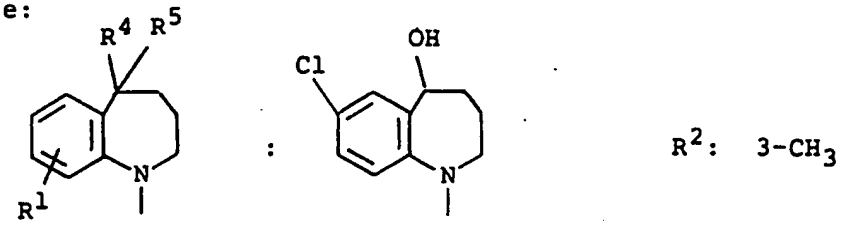
Recrystallization solvent: Methanol/diethyl ether

Melting point: 210 - 211°C

Form: Free

Example 38

Structure:



R^2: 3-CH_3

R^3: 4-$NHCOCH_2$-(2-Cl-phenyl)

Crystalline form: White powder

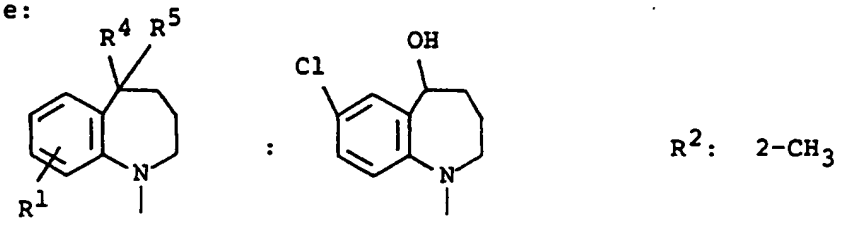
Recrystallization solvent: Methanol

Melting point: 217 - 218°C

Form: Free

Example 39

Structure:



R^2: 2-CH_3

R^3: 4-$NHCOCH_2$-(2-Cl-phenyl)

Crystalline form: White powder

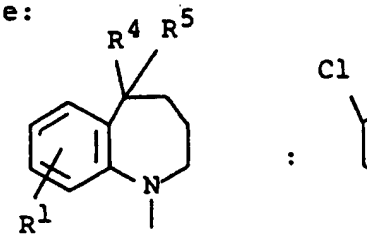
Recrystallization solvent: Methanol

Melting point: 245 - 247°C

Form: Free

Example 40

Structure:



R^2: 2-OCH_3

R^3: 4-$NHCOCH_2$-

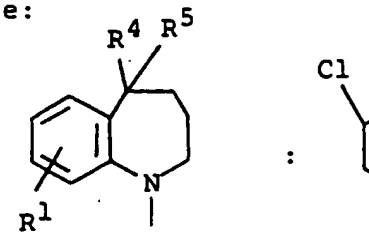
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 25)

Example 41

Structure:



R^2: 2-Cl

R^3: 4-$NHCOCH_2$-

Crystalline form: White powder

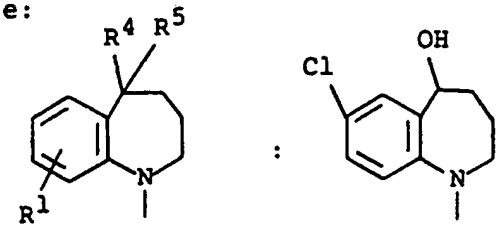
Recrystallization solvent: Methanol/diethyl ether

Melting point: 214 - 216°C

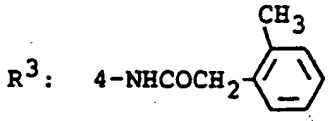
Form: Free

Example 42

Structure:



R^2: 3-F



R^3: 4-NHCOCH$_2$-

Crystalline form: White powder

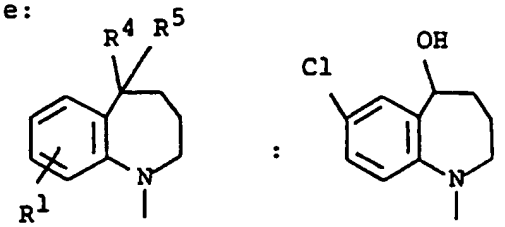
Recrystallization solvent: Methanol

Melting point: 208.5 - 209°C

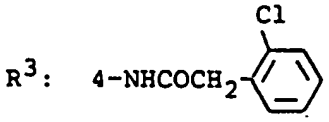
Form: Free

Example 43

Structure:



R^2: 3-F



R^3: 4-NHCOCH$_2$-

Crystalline form: White powder

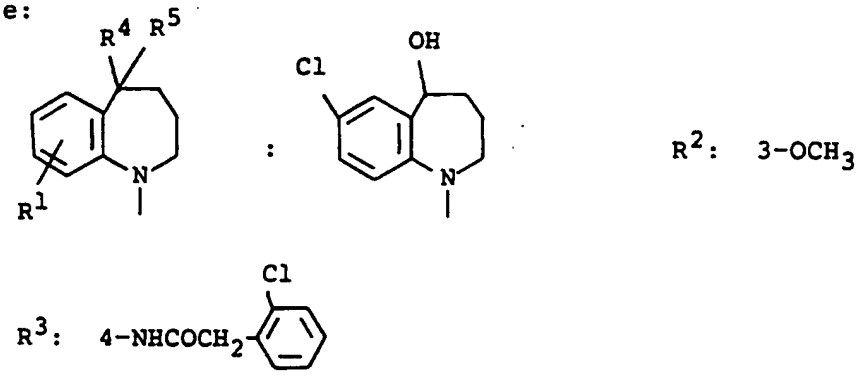
Recrystallization solvent: Methanol

Melting point: 184.0- 186°C

Form: Free

Example 44

Structure:



Crystalline form: White powder

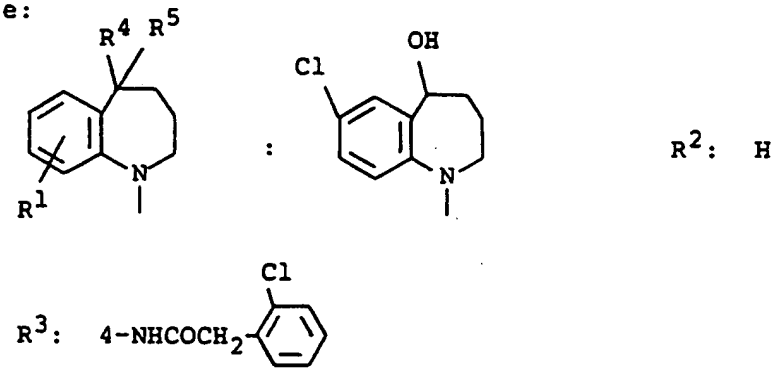
Recrystallization solvent: Methanol/diethyl ether

Melting point: 195 - 196°C

Form: Free

Example 45

Structure:



Crystalline form: White powder

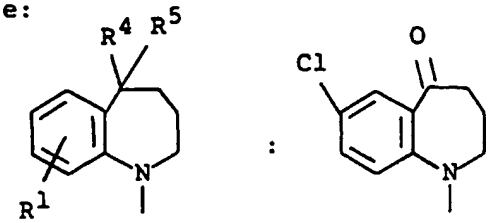
Recrystallization solvent: Methanol/diethyl ether

Melting point: 214 - 215°C

Form: Free

Example 46

Structure:



R^2: 2-CH_3

Crystalline form: White powder

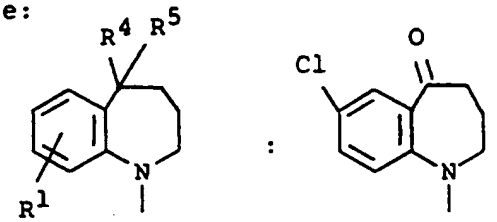
Recrystallization solvent: Methanol/diethyl ether

Melting point: 145 - 146.5°C

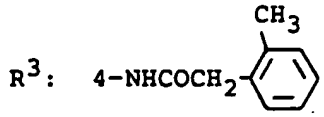
Form: Free

Example 47

Structure:



R^2: 2-OCH_3



Crystalline form: White powder

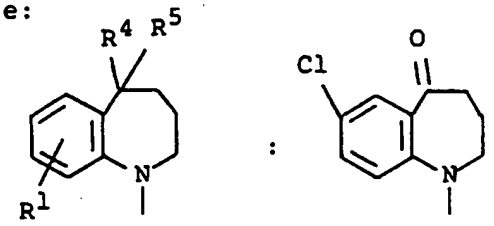
Recrystallization solvent: Methanol/diethyl ether

Melting point: 241 - 241.5°C

Form: Free

Example 48

Structure:



R^2: 3-CH_3

Crystalline form: White powder

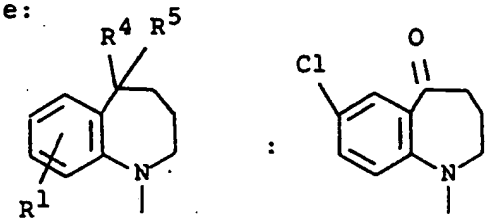
Recrystallization solvent: Methanol/diethyl ether

Melting point: 119 - 120°C

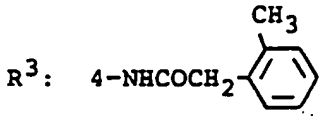
Form: Free

Example 49

Structure:



R^2: 3-OCH_3



Crystalline form: White powder

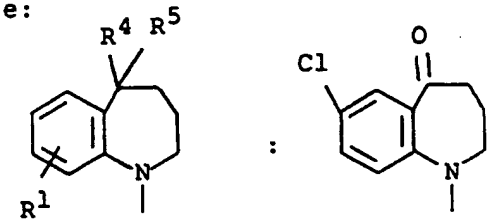
Recrystallization solvent: Methanol/diethyl ether

Melting point: 142.5 - 146.5°C

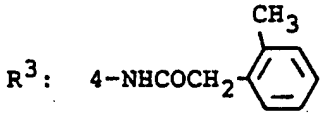
Form: Free

Example 50

Structure:



R^2: 3-F



Crystalline form: White powder

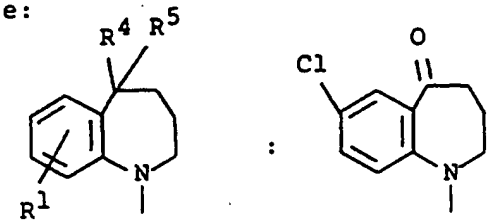
Recrystallization solvent: Methanol/diethyl ether

Melting point: 145 - 146°C

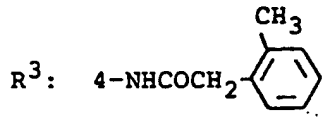
Form: Free

Example 51

Structure:



R^2: 2-F



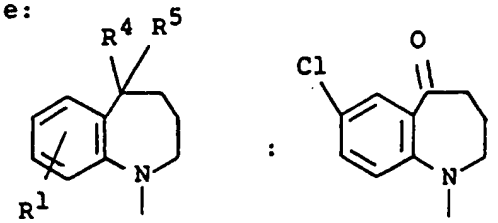
Crystalline form: Colorless amorphous

Form: Free

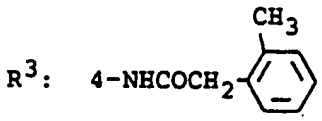
NMR analysis: 26)

Example 52

Structure:



R^2: 2-Cl



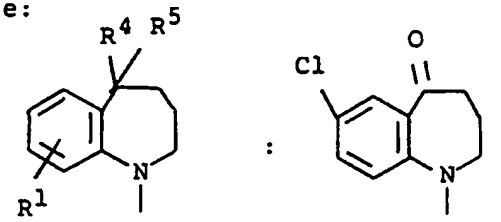
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 27)

Example 53

Structure:



R^2: H

Crystalline form: White powder

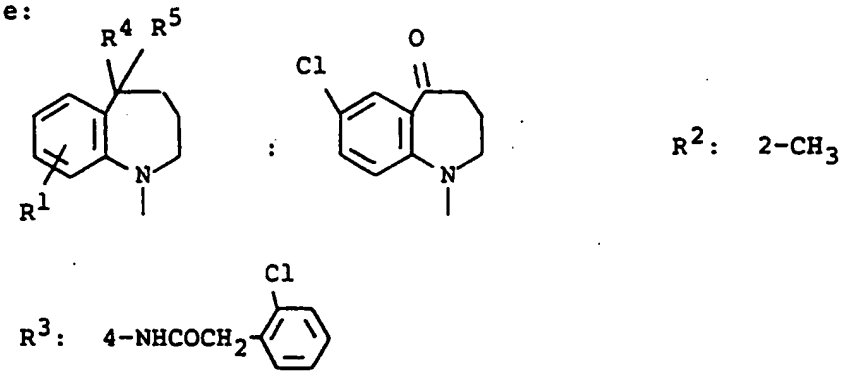
Recrystallization solvent: Methanol/diethyl ether

Melting point: 199 - 202°C

Form: Free

Example 54

Structure:



Crystalline form: White powder

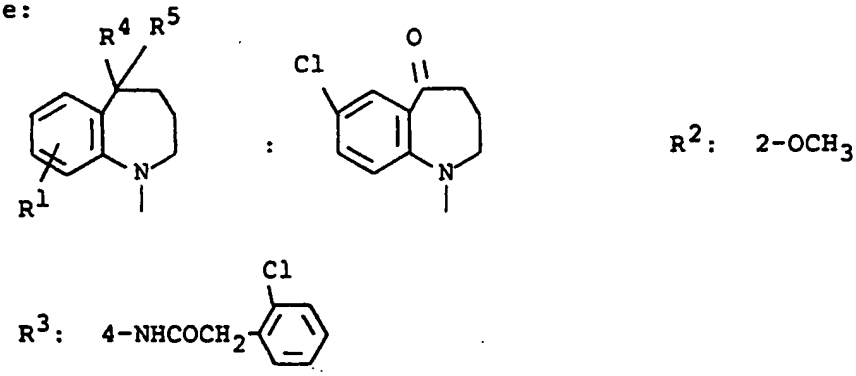
Recrystallization solvent: Methanol/diethyl ether

Melting point: 171 - 172°C

Form: Free

Example 55

Structure:



Crystalline form: White powder

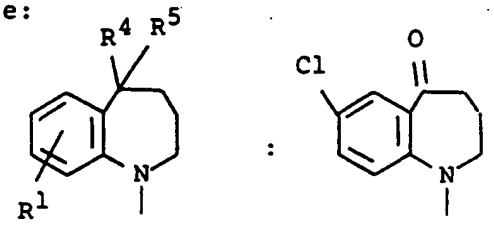
Recrystallization solvent: Methanol/diethyl ether

Melting point: 243.5 - 245°C

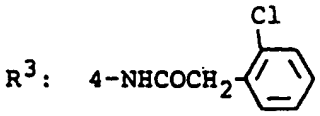
Form: Free

Example 56

Structure:



R^2: 2-Cl



Crystalline form: White powder

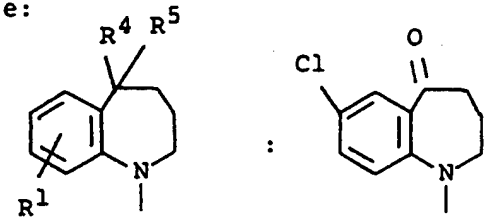
Recrystallization solvent: Methanol/diethyl ether

Melting point: 239 - 240°C

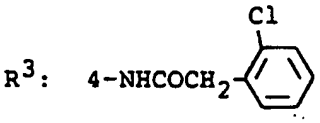
Form: Free

Example 57

Structure:



R^2: 2-F



Crystalline form: White powder

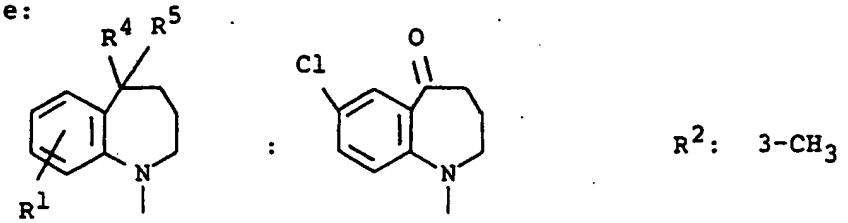
Recrystallization solvent: Methanol/diethyl ether

Melting point: 162 - 163°C

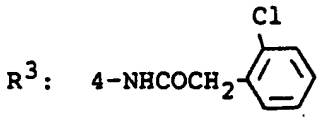
Form: Free

Example 58

Structure:



R^2: 3-CH_3



Crystalline form: White powder

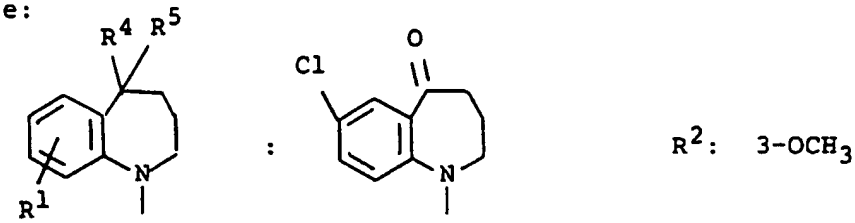
Recrystallization solvent: Methanol/diethyl ether

Melting point: 134 - 135°C

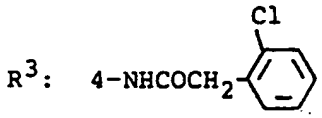
Form: Free

Example 59

Structure:



R^2: 3-OCH_3



Crystalline form: White powder

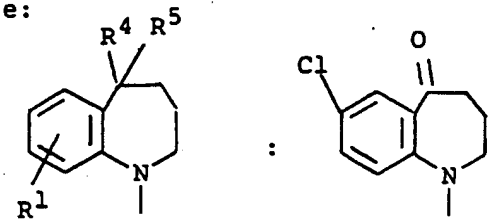
Recrystallization solvent: Methanol/diethyl ether

Melting point: 177 - 178°C

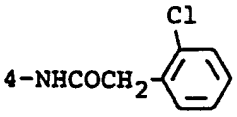
Form: Free

Example 60

Structure:



R^2: 3-F

R^3: 

Crystalline form: White powder

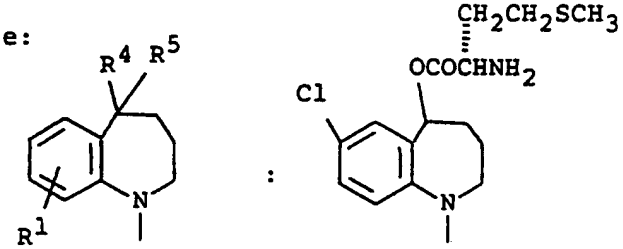
Recrystallization solvent: Methanol/diethyl ether

Melting point: 168 - 169°C

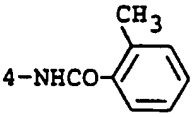
Form: Free

Example 61

Structure:



R^2: 2-OCH_3

R^3: 

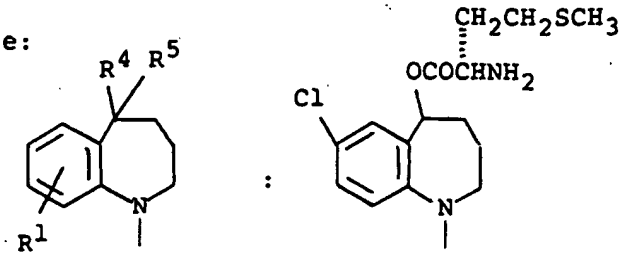
Crystalline form: Colorless amorphous

Form: Free

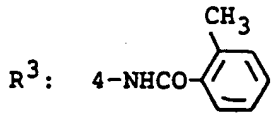
NMR analysis: 28)

Example 62

Structure:



R^2: 2-OCH_3



R^3: 4-NHCO-

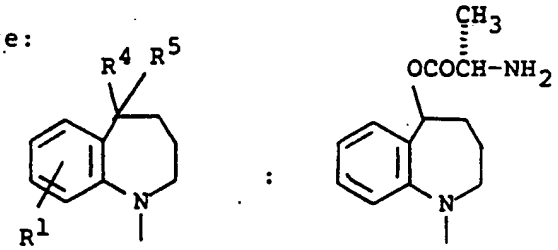
Crystalline form: Colorless amorphous

Form: Free

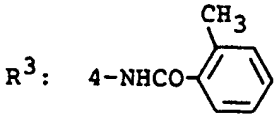
NMR analysis: 29)

Example 63

Structure:



R^2: 2-Cl



R^3: 4-NHCO-

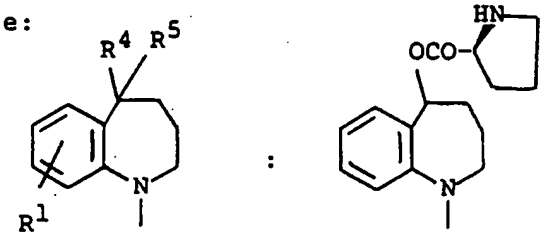
Crystalline form: Colorless amorphous

Form: Free

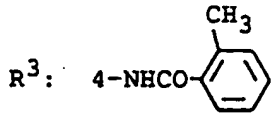
NMR analysis: 30)

Example 64

Structure:



R^2: 2-Cl



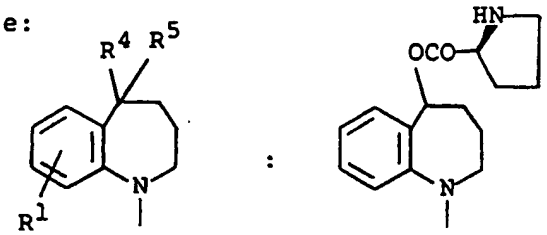
Crystalline form: Colorless amorphous

Form: Free

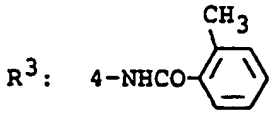
NMR analysis: 31)

Example 65

Structure:



R^2: 2-Cl



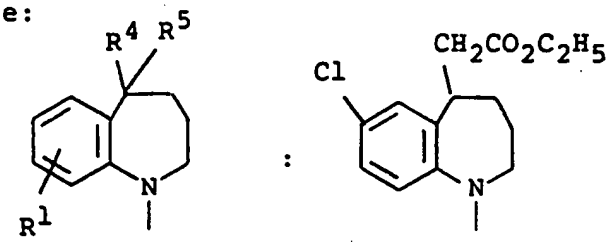
Crystalline form: Colorless amorphous

Form: Free

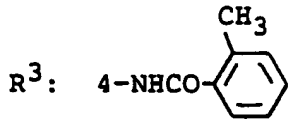
NMR analysis: 32)

Example 66

Structure:



R^2: 2-CH_3



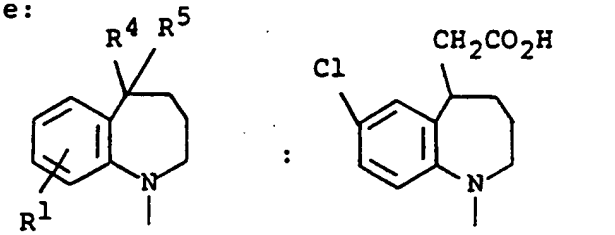
Crystalline form: Colorless amorphous

Form: Free

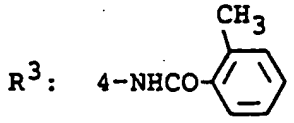
NMR analysis: 33)

Example 67

Structure:



R^2: 2-CH_3



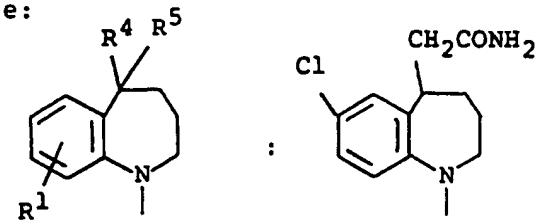
Crystalline form: Colorless amorphous

Form: Free

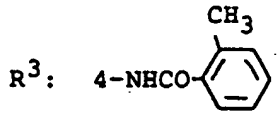
NMR analysis: 34)

Example 68

Structure:



R^2: 2-CH_3



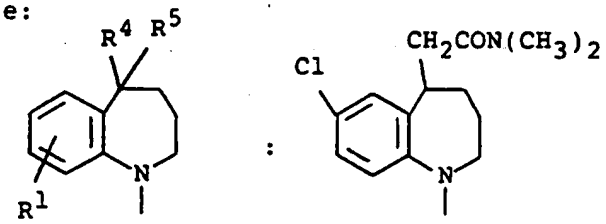
Crystalline form: Colorless amorphous

Form: Free

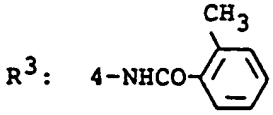
NMR analysis: 35)

Example 69

Structure:



R^2: 2-CH_3



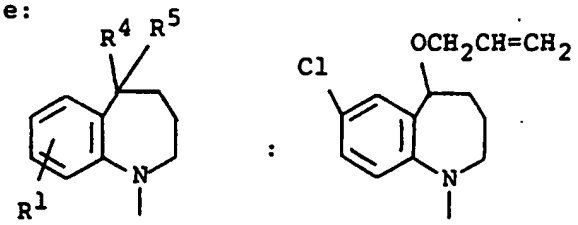
Crystalline form: Colorless amorphous

Form: Free

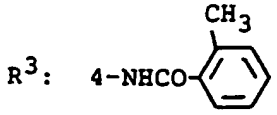
NMR analysis: 36)

Example 70

Structure:



R^2: 2-CH_3



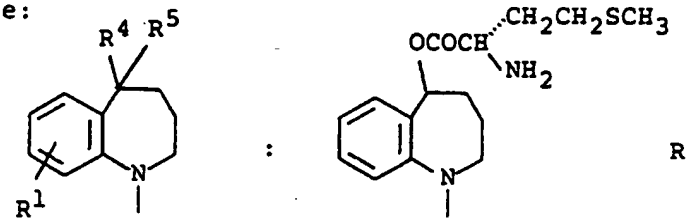
Crystalline form: Colorless amorphous

Form: Free

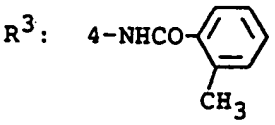
NMR analysis: 37)

Example 71

Structure:



R^2: 2-Cl



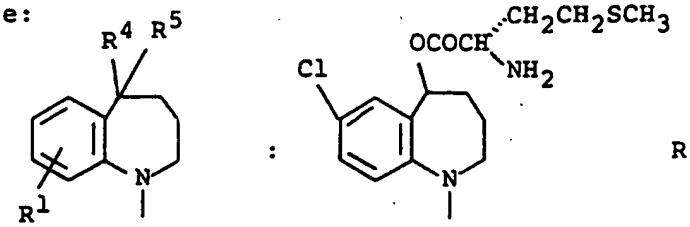
Crystalline form: Colorless amorphous

Form: Free

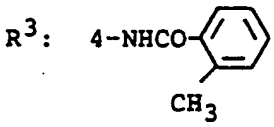
NMR analysis: 38)

Example 72

Structure:



R^2: 2-CH_3



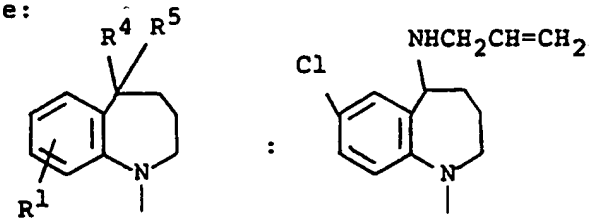
Crystalline form: Colorless amorphous

Form: Free

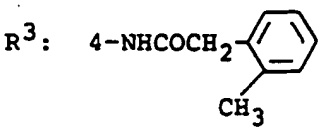
NMR analysis: 39)

Example 73

Structure:



R^2: H



Crystalline form: White powder

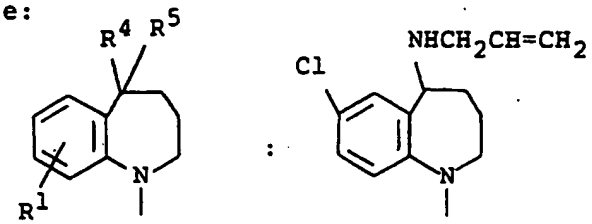
Recrystallization solvent: Methanol/diethyl ether

Melting point: 128 - 130°C

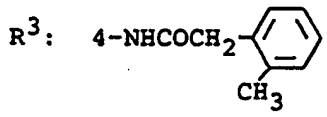
Form: Free

Example 74

Structure:



R^2: 2-CH_3



Crystalline form: White powder

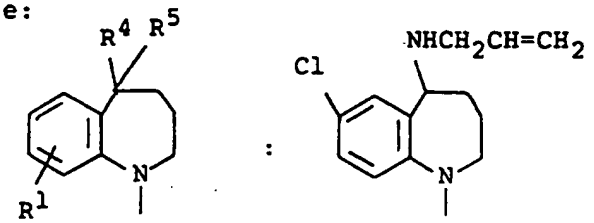
Recrystallization solvent: Methanol/diethyl ether

Melting point: 139 - 140°C

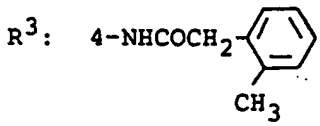
Form: Free

Example 75

Structure:



R^2: 2-OCH_3



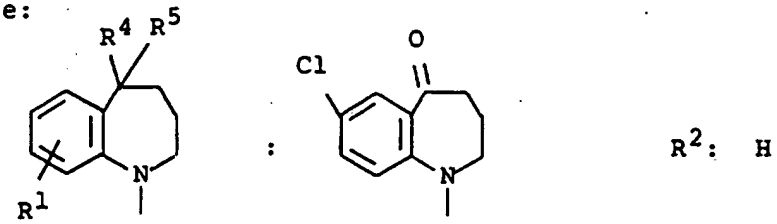
Crystalline form: Colorless amorphous

Form: Free

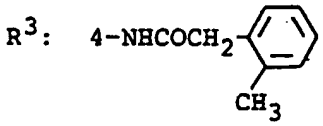
NMR analysis: 40)

Example 76

Structure:



R^2: H



Crystalline form: White powder

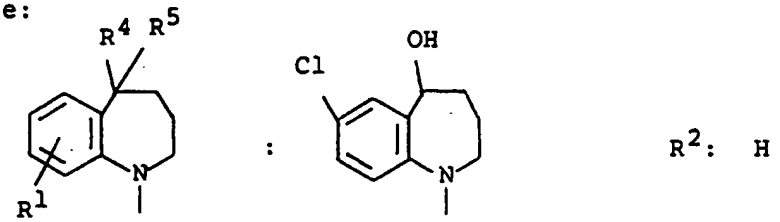
Recrystallization solvent: Methanol/diethyl ether

Melting point: 194 - 196°C

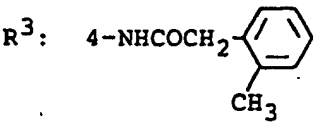
Form: Free

Example 77

Structure:



R^2: H



Crystalline form: White powder

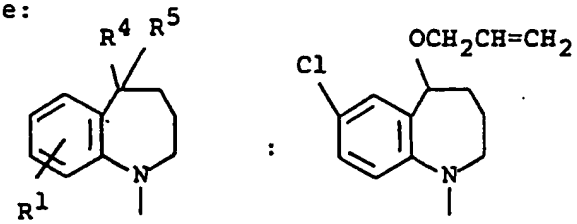
Recrystallization solvent: Methanol/diethyl ether

Melting point: 241 - 243°C

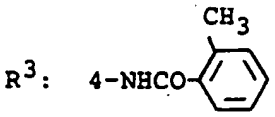
Form: Free

Example 78

Structure:



R^2: H



Crystalline form: White powder

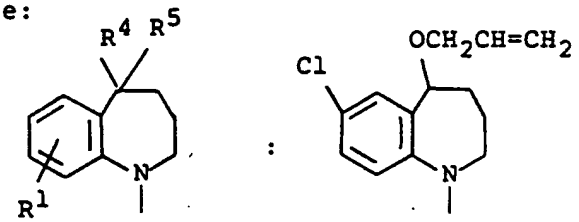
Recrystallization solvent: Dichloromethane/diethyl ether

Melting point: 129.5 - 131.5°C

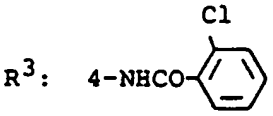
Form: Free

Example 79

Structure:



R^2: H



Crystalline form: White powder

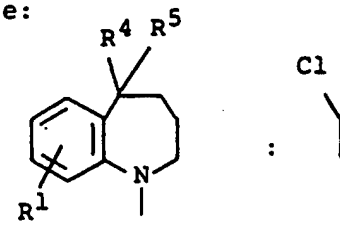
Recrystallization solvent: Dichloromethane/diethyl ether

Melting point: 136 - 138°C

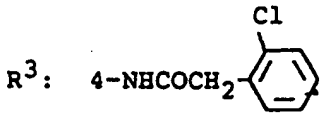
Form: Free

Example 80

Structure:



R^2: 2-Cl



Crystalline form: White powder

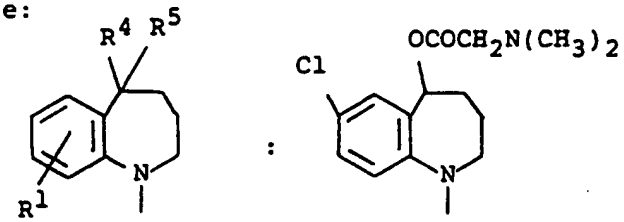
Recrystallization solvent: Methanol/diethyl ether

Melting point: 178 - 179°C

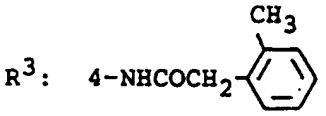
Form: Free

Example 81

Structure:



R^2: 2-CH_3



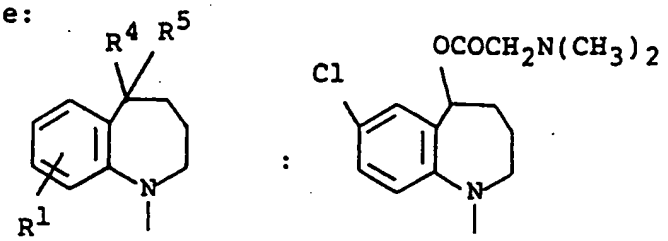
Crystalline form: Colorless amorphous

Form: Free

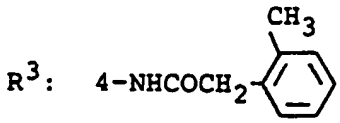
NMR analysis: 41)

Example 82

Structure:



R^2: 3-CH_3



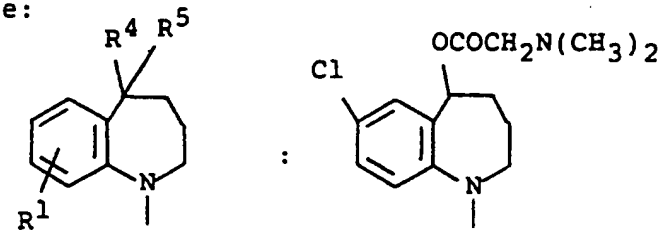
Crystalline form: Colorless amorphous

Form: Free

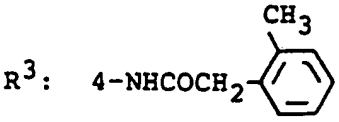
NMR analysis: 42)

Example 83

Structure:



R^2: 2-OCH_3



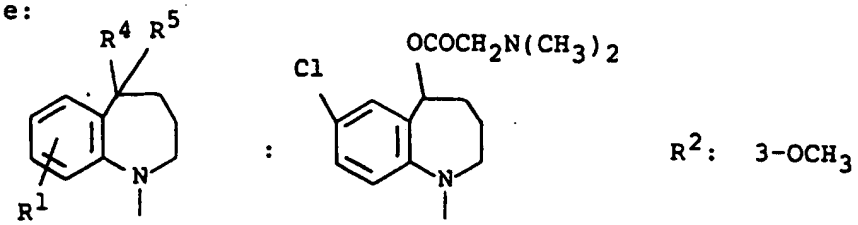
Crystalline form: Colorless amorphous

Form: Free

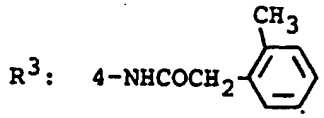
NMR analysis: 43)

Example 84

Structure:



R^2: 3-OCH_3



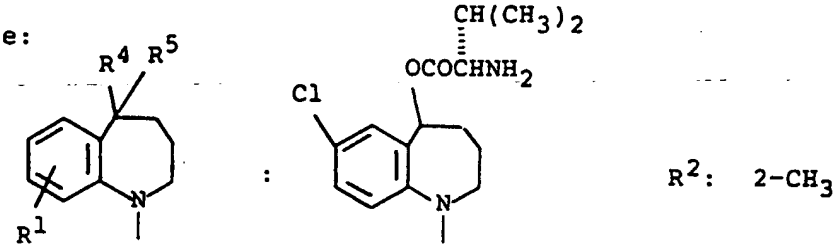
Crystalline form: Colorless amorphous

Form: Free

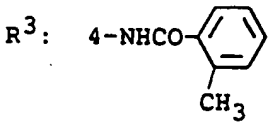
NMR analysis: 44)

Example 85

Structure:



R^2: 2-CH_3



Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 45)

1) ^{1}H-NMR ($CDCl_3$) δ ; 1.41 - 1.72 (2H, m), 1.86 - 2.13 (1H, m), 2.19 - 2.48 (1H, m), 2.64 - 3.18 (4H, m), 4.20 - 4.83 (2H, m), 6.44 - 7.10 (3H, m), 7.17 - 8.15 (7H, m), 9.32 (1H, brs), 9.91 (1H, s), 10.72 (1H, s)

2) ^{1}H-NMR ($CDCl_3$) δ ; 1.40 - 3.20 (11H, m), 3.27 - 5.05 (2H, m), 6.38 - 8.37 (11H, m)

3) ^{1}H-NMR ($CDCl_3$) δ ; 1.40 - 3.30 (14H, m), 3.30 - 5.20 (2H, m), 6.70 - 8.60 (11H, m)

4) ^{1}H-NMR ($CDCl_3$) δ ; 1.47 - 5.16 (7H, m), 6.30 - 8.23 (11H, m), 8.90 - 9.10 (1H, m), 10.10 - 10.55 (1H, m)

5) ^{1}H-NMR (DMSO-d_6) δ ; 1.30 - 5.28 (9H, m), 6.19 - 8.13 (11H, m), 9.44 - 9.60 (1H, m), 10.56 - 10.94 (1H, m)

6) ^{1}H-NMR ($CDCl_3$) δ ; 1.46 - 5.10 (21H, m), 6.43 - 8.44 (11H, m)

7) ^{1}H-NMR ($CDCl_3$) δ ; 1.00 - 2.55 (10H, m), 2.33 (3H, s), 2.57 - 3.14 (1H, m), 3.39 - 3.78 (1H, m), 3.61 (2H, s), 3.84 - 5.20 (1H, m), 6.40 - 7.71 (12H, m)

8) ^{1}H-NMR ($CDCl_3$) δ ; 1.05 - 2.57 (10H, m), 2.35 (3H, s), 2.57 - 3.15 (1H, m), 3.30 - 3.82 (1H, m), 3.63 (2H, s), 3.89 - 5.19 (1H, m), 6.42 - 7.70 (12H, m)

9) ^{1}H-NMR ($CDCl_3$) δ ; 1.10 - 3.18 (11H, m), 3.32 - 3.80 (1H, m), 3.57 (2H, s), 3.95 - 5.20 (1H, m), 6.43 - 7.68 (12H, m), 8.13 - 8.44 (1H, m)

10) ^{1}H-NMR ($CDCl_3$) δ ; 1.06 - 3.21 (11H, m), 3.31 - 3.90 (1H, m), 3.54 (2H, s), 3.90 - 5.18 (1H, m), 6.38 - 7.65 (12H, m), 8.26 - 8.62 (1H, m)

11) ^{1}H-NMR ($CDCl_3$) δ ; 1.10 - 3.14 (11H, m), 3.34 - 3.75 (1H, m), 3.65 (2H, s), 3.89 (3H, s), 3.95 - 5.20 (1H, m), 6.45 - 7.70 (12H, m), 7.72 - 8.05 (1H, m)

12) ^{1}H-NMR ($CDCl_3$) δ ; 1.09 - 3.16 (11H, m), 3.35 - 5.20 (2H, m), 3.61 (2H, s), 3.78 (3H, s), 6.38 - 7.64 (12H, m), 7.70 (1H, s)

13) ^{1}H-NMR ($CDCl_3$) δ ; 1.10 - 3.25 (11H, m), 3.36 - 3.71 (3H, m), 3.75 - 3.90 (3H, m), 3.95 - 5.20 (1H, m), 6.42 - 7.68 (12H, m)

14) ^{1}H-NMR ($CDCl_3$) δ ; 1.08 - 3.21 (11H, m), 3.36 - 3.79 (1H, m), 3.59 (2H, s), 3.91 - 5.19 (1H, m), 6.45 - 7.65 (12H, m), 8.04 - 8.35 (1H, m)

15) ^{1}H-NMR ($CDCl_3$) δ ; 1.08 - 3.20 (11H, m), 3.34 - 3.79 (1H, m), 3.58 (2H, s), 3.90 - 5.19 (1H, m), 6.43 - 7.65 (12H, m), 7.91 - 8.20 (1H, m)

16) ^{1}H-NMR ($CDCl_3$) δ ; 1.11 - 3.13 (11H, m), 3.35 - 3.72 (1H, m), 3.61 (2H, s), 3.86 (3H, s), 3.88 (3H, s), 3.94 - 5.20 (1H, m), 6.45 - 7.69 (11H, m)

17) ^{1}H-NMR ($CDCl_3$) δ ; 1.10 - 3.27 (11H, m), 3.36 - 3.75 (1H, m), 3.49 (2H, s), 3.90 - 5.20 (1H, m), 6.41 - 7.84 (11H, m), 8.81 - 9.59 (1H, m)

18) ^{1}H-NMR ($CDCl_3$) δ ; 1.10 - 3.20 (11H, m), 3.35 -

3.66 (1H, m), 3.73 (2H, s), 3.91 - 5.20 (1H, m), 6.48 - 7.65 (11H, m), 7.68 - 7.94 (1H, m)

19) ^{1}H-NMR ($CDCl_3$) δ ; 1.08 - 3.21 (11H, m), 3.38 - 3.68 (1H, m), 4.00 (2H, s), 3.95 - 5.20 (1H, m), 6.45 - 7.70 (11H, m), 8.15 (1H, s)

20) ^{1}H-NMR ($CDCl_3$) δ ; 1.08 - 3.25 (11H, m), 3.36 - 3.69 (1H, m), 3.91 (2H, s), 3.88 - 5.20 (1H, m), 6.45 - 7.72 (11H, m), 7.85 - 8.13 (1H, m), 8.85 (1H, s)

21) ^{1}H-NMR ($CDCl_3$) δ ; 1.10 - 3.30 (11H, m), 3.39 - 3.95 (3H, m), 3.95 - 5.20 (1H, m), 6.45 - 7.82 (10H, m), 7.94 - 8.36 (2H, m), 8.82 - 9.17 (1H, m)

22) ^{1}H-NMR ($CDCl_3$) δ ; 1.06 - 3.11 (11H, m), 3.35 - 3.70 (1H, m), 3.62 (2H, s), 3.74 (3H, s), 3.86 (3H, s), 3.92 - 5.20 (1H, m), 6.45 - 7.67 (11H, m), 7.81 - 8.16 (1H, m)

23) ^{1}H-NMR ($CDCl_3$) δ ; 1.04 - 5.10 (17H, m), 5.96 - 6.17 (1H, m), 6.52 - 7.86 (11H, m)

24) ^{1}H-NMR ($CDCl_3$) δ ; 1.41 - 1.89 (2H, m), 1.90 - 2.24 (2H, m), 2.31 (3H, s), 2.47 - 2.89 (2H, m), 3.45 (3H, s), 3.69 (2H, s), 4.57 - 5.13 (2H, m), 6.39 - 6.76 (2H, m), 6.78 - 6.95 (1H, m), 6.95 - 7.41 (7H, m), 7.41 - 7.65 (1H, m)

25) ^{1}H-NMR ($CDCl_3$) δ ; 1.45 - 1.92 (2H, m), 1.92 - 2.28 (2H, m), 2.50 - 2.96 (2H, m), 3.45 (3H, s), 3.81 (2H, s), 4.64 - 5.20 (2H, m), 6.28 - 7.12 (3H, m),

7.13 - 7.50 (5H, m), 7.50 - 7.64 (1H, m), 7.65 - 7.99 (1H, m)

26) ^{1}H-NMR ($CDCl_3$) δ ; 1.52 - 2.54 (2H, m), 2.27 (3H, s), 2.70 - 2.98 (2H, m), 2.98 - 5.52 (2H, m), 3.65 (2H, s), 6.56 - 6.87 (1H, m), 6.97 - 7.43 (8H, m), 7.78 (1H, d, J=2.4 Hz), 7.91 - 8.15 (1H, m)

27) ^{1}H-NMR ($CDCl_3$) δ ; 1.76 - 2.40 (2H, m), 2.29 (3H, s), 2.86 (2H, t, J=6.0 Hz), 3.00 - 5.32 (2H, m), 3.69 (2H, s), 6.46 - 8.05 (10H, m)

28) ^{1}H-NMR ($CDCl_3$) δ ; 1.47 - 2.92, 3.44 - 4.11 (total 21H, m), 4.66 - 5.12 (1H, m), 5.85 - 6.30 (1H, m), 6.61 - 8.10 (11H, m)

$[\alpha]_D^{24}$ = +90° (methanol, c=0.2)
(measured as hydrochloride)

29) ^{1}H-NMR ($CDCl_3$) δ ; 1.48 - 2.88, 3.45 - 4.09 (total 21H, m), 4.60 - 5.05 (1H, m), 5.85 - 6.31 (1H, m), 6.62 - 7.78 (10H, m), 7.92 - 8.41 (1H, m)

$[\alpha]_D^{24}$ = -107° (methanol, c=0.2)
(measured as hydrochloride)

30) ^{1}H-NMR ($CDCl_3$) δ ; 1.21 - 3.06, 3.40 - 3.87 (total 14H, m), 4.54 - 5.05 (1H, m), 5.88 - 6.22 (1H, m), 6.83 - 8.09, 8.33 - 8.59, 8.82 - 9.03 (total 12H, m)

$[\alpha]_D^{24}$ = +90°C (methanol, c=0.2)
(measured as hydrochloride)

31) ^{1}H-NMR ($CDCl_3$) δ ; 1.50 - 3.22, 3.54 - 3.99 (total 16H, m), 4.41 - 4.90 (1H, m), 5.88 - 6.22 (1H, m),

6.79 - 8.04 (11H, m), 9.05 - 9.63 (1H, m)

$[\alpha]_D^{24}$ = +54° (methanol, c=0.2)
(measured as hydrochloride)

32) ^{1}H-NMR ($CDCl_3$) δ ; 1.51 - 4.12 (16H, m), 4.60 - 5.17 (1H, m), 5.89 - 5.29 (1H, m), 6.71 - 8.50, 9.85 - 10.36 (total 12H, m)

$[\alpha]_D^{24}$ = -68° (methanol, c=0.2)
(measured as hydrochloride)

33) ^{1}H-NMR ($CDCl_3$) δ ; 1.04 - 4.63 (20H, m), 6.42 - 7.74 (11H, m)

34) ^{1}H-NMR (DMSO-d_6) δ ; 1.08 - 2.23 (4H, m), 2.23 - 2.55 (6H, m), 2.55 - 3.00 (3H, m), 3.00 - 5.10 (3H, m), 6.68 - 7.90 (10H, m), 10.13 - 10.50 (1H, m)

35) ^{1}H-NMR ($CDCl_3$) δ ; 1.49 - 2.43 (3H, m), 2.43 - 2.61 (6H, m), 2.61 - 2.92 (2H, m), 2.92 - 3.99 (3H, m), 4.48 - 4.97 (1H, m), 5.80 (1H, brs), 6.44 (1H, brs), 6.53 - 7.83 (11H, m)

36) ^{1}H-NMR ($CDCl_3$) δ ; 1.43 - 2.38 (3H, m), 2.38 - 2.77 (8H, m), 2.77 - 3.33 (8H, m), 3.33 - 5.10 (2H, m), 6.36 - 8.04 (11H, m)

37) ^{1}H-NMR ($CDCl_3$) δ ; 1.43 - 2.13 (2H, m), 2.13 - 2.63 (7H, m), 2.63 - 3.75 (2H, m), 3.75 - 4.82 (4H, m), 4.97 - 5.50 (2H, m), 5.83 - 6.15 (1H, m), 6.51 - 7.73 (11H, m)

38) Isomer A: Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 0.95 - 4.18, 4.61 - 5.18 (total 19H, m), 5.85 - 6.29 (1H, m), 6.90 - 8.35 (12H, m)

Isomer B: Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 0.94 - 4.33, 4.61 - 5.23 (total 19H, m), 5.84 - 6.28 (1H, m), 6.76 - 7.91 (11H, m), 9.25 - 9.76 (1H, m)

39) Isomer A: Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.46 - 2.98, 3.22 - 4.05 (total 21H, m), 4.67 - 5.19 (1H, m), 5.79 - 6.22 (1H, m), 6.50 - 7.81 (11H, m)

$[\alpha]_D^{24}$ = +112° (methanol, c=0.2)
(measured as hydrochloride)

Isomer B: Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 1.42 - 2.98, 3.30 - 4.01 (total 21H, m), 4.58 - 5.20 (1H, m), 5.85 - 6.21 (1H, m), 6.43 - 8.14 (11H, m)

$[\alpha]_D^{24}$ = -143° (methanol, c=0.2)
(measured as hydrochloride)

40) ^{1}H-NMR ($CDCl_3$) δ ; 1.30 - 2.30 (4H, m), 2.31 (3H, s), 2.95 - 3.54 (3H, m), 2.71 (2H, s), 2.80 - 4.60 (2H, m), 5.01 - 5.39 (2H, m), 5.70 - 6.05 (1H, m), 6.41 - 6.63 (1H, m), 6.80 - 7.43 (9H, m), 7.50 - 7.67 (1H, m)

41) ^{1}H-NMR ($CDCl_3$) δ ; 1.49 - 1.97 (2H, m), 2.02 - 2.30 (2H, m), 2,30 - 2.61 (12H, m), 2.68 - 2.95 (1H, m), 3.11 - 3.49 (2H, m), 3.62 - 3.86 (2H, m), 4.68 - 5.15 (1H, m), 5.90 - 6.19 (1H, m), 6.41 - 6.60 (1H, m), 6.60 - 7.02 (3H, m), 7.05 - 7.40 (6H, m), 7.40 - 7.52 (1H, m)

42) ^{1}H-NMR ($CDCl_3$) δ ; 1.55 - 1.94 (2H, m), 1.95 - 2.59 (14H, m), 2.60 - 2.91 (1H, m), 2.91 - 3.47 (2H, m), 3.75 (2H, s), 4.60 - 5.20 (1H, m), 5.90 - 6.22 (1H, m), 6.40 - 6.66 (1H, m), 6.72 - 7.41 (9H, m), 7.77 - 8.04 (1H, m)

43) ^{1}H-NMR ($CDCl_3$) δ ; 1.53 - 1.94 (2H, m), 2.00 - 2.25 (2H, m), 2.25 - 2.52 (9H, m), 2.58 - 2.92 (1H, m), 3.07 - 3.41 (2H, m), 3.53 (3H, s), 3.60 - 3.91 (2H, m), 4.66 - 5.13 (1H, m), 6.39 - 7.55 (10H, m), 7.60 - 7.80 (1H, m)

44) ^{1}H-NMR ($CDCl_3$) δ ; 1.62 - 1.98 (2H, m), 1.98 - 2.58 (11H, m), 2.64 - 2.98 (1H, m), 2.99 - 3.44 (2H, m), 3.44 - 3.60 (3H, m), 3.72 (2H, s), 4.60 - 5.21 (1H, m), 5.91 - 6.28 (1H, m), 6.44 - 7.10 (4H, m), 7.10 - 7.49 (5H, m), 7.72 (1H, s), 8.00 - 8.36 (1H, m)

45) Isomer A: Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 0.67 - 3.62, 4.67 - 5.20 (total 22H, m), 5.87 - 6.31 (1H, m), 6.49 - 7.85 (11H, m)

$[\alpha]_D^{24}$ = -133° (methanol, c=0.2)
(measured as hydrochloride)

Isomer B: Colorless amorphous

^{1}H-NMR ($CDCl_3$) δ ; 0.81 - 3.65, 4.65 - 5.18 (total 22H, m), 5.86 - 6.28 (1H, m), 6.44 - 8.03 (11H, m)

$[\alpha]_D^{24}$ = +126° (methanol, c=0.2)
(measured as hydrochloride)

Example 86

To tetrahydrofuran (200 ml) is added sodium hydride (60 %, 0.85 g), and thereto is added dropwise ethyl diethylphosphonoacetat (4.68 ml) with stirring under ice-cooling, and th mixtur is further stirred under ice-cooling for 10 minutes. To the reaction mixture is added 5-oxo-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine (2.10 g), and the mixture is stirred at room temperature for 6 hours. Th reaction solution is poured into ice-water (200 ml), and extracted with ethyl acetate (300 ml). The xtract is wash d with brine (300 ml), dried ov r magnesium sulfate, and th solv nt

is distilled off. The resulting residue is purified by silica gel column chromatography (luent; thyl acetate : n-hexane = 1 : 2) to give 5-thoxycarbonylmethylidene-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)-benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine (2.22 g) in the form of a mixture of the E-type compound and the Z-type compound thereof, as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ ; 1.04 - 5.10 (17H, m), 5.96 - 6.17 (1H, m), 6.52 - 7.86 (11H, m)

Example 87

5-Ethoxycarbonylmethylidene-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.30 g) and nickel chloride hexahydrate (0.55 g) are dissolved in a mixture of tetrahydrofuran/methanol (1:1) (30 ml), and to the mixture is added slowly sodium borohydride (0.26 g) with stirring under ice-cooling, and then the mixture is further stirred for 10 minutes under ice-cooling. The insoluble materials are filtered with Celite, and the filtrate is concentrated. The resulting residue is purified by silica gel column chromatography (eluent; ethyl acetate : n-hexane = 1 : 1) to give 5-ethoxycarbonylmethyl-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.13 g) as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ ; 1.04 - 4.63 (20H, m), 6.42 - 7.74 (11H, m)

Example 88

To a solution of 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.0 g), dimethylaminopyridine (1.26 g) and dimethylaminopyridine hydrochloride (1.10 g) in chloroform (20 ml) are added N-benzyloxycarbonyl-L-valine (672 mg) and dicyclohexylcarbodiimide (1.42 g), and the mixture is stirred at room temperature for 7 hours. To the mixture are added methanol (3 ml) and acetic acid (0.7 ml), and the mixture is stirred at room temperature for 30 minutes. The insoluble materials are removed by filtration, and to the filtrate is added 5 % aqueous sodium hydrogen sulfate solution, and further extracted with dichloromethane. The extract is washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and the solvent is distilled off under reduced pressure to give crude 5-N-benzyloxycarbonyl-L-valyloxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)-benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine (2.0 g). This product is dissolved in a mixture of acetic acid (15 ml) and ethyl acetate (15 ml), and thereto is added 5 % Pd-C (0.3 g). The mixture is subjected to hydrogenation at ordinary room temperature under atmospheric pressure. After hydrogenation, the catalyst is removed by filtration, and the filtrate is concentrated. The resulting residue is purified by silica gel column chromatography (eluent; ethyl acetate) to give Isomer A (0.48 g) and Isomer B (0.47 g) of 5-L-valyloxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)-benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

Isomer A:

Rf value: 0.3 (developer; ethyl acetate:methanol = 10:1)

^{1}H-NMR ($CDCl_3$) δ ; 0.67 - 3.62, 4.67 - 5.20 (total 22H, m), 5.87 - 6.31 (1H, m), 6.49 - 7.85 (11H, m)

$[\alpha]_D^{24}$ = 133° (methanol, c = 0.2) (measured as hydrochloride)

Isomer B:

Rf value: 0.4 (developer; ethyl acetate:methanol = 10:1)

^{1}H-NMR ($CDCl_3$) δ ; 0.81 - 3.65, 4.65 - 5.18 (total 22H, m), 5.86 - 6.28 (1H, m), 6.44 - 8.03 (11H, m)

$[\alpha]_D^{24}$ = +126° (methanol, c = 0.2) (measured as hydrochloride)

Example 89

A uniform solution of 5-(N-tert-butoxycarbonyl-L-methionyloxy)-7-chloro-1-[2-methoxy-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydr -1H-benzazepine (1.27 g), trifluoroacetic acid (2.5 ml) and anisole (0.6 ml) is stirred at room temperature for 2 hours. The trifluoroacetic acid is almost distilled off under reduced pressure, and the residue is acidified with an 0.2 N aqueous sodium hydroxide solution, and the mixture is extracted with dichloromethane. The dichloromethane layer is washed with water, dried over magnesium sulfate and concentrated. The resulting residue is purified by silica gel column chromatography (eluent; ethyl acetate) to give Isomer A (0.34 g) and Isomer B (0.35 g) of 5-(L-methionyloxy)-7-chloro-1-[2-methoxy-

4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

Isomer A: Colorless amorphous

Rf value: 0.5 (developer; ethyl acetate:methanol = 10:1)
^{1}H-NMR ($CDCl_3$) δ ; 1.47 - 2.92, 3.44 - 4.11 (total 21H, m), 4.66 - 5.12 (1H, m), 5.85 - 6.30 (1H, m), 6.61 - 8.10 (11H, m)
$[\alpha]_D^{24}$: +96° (methanol, c = 0.2) (measured as hydrochloride)

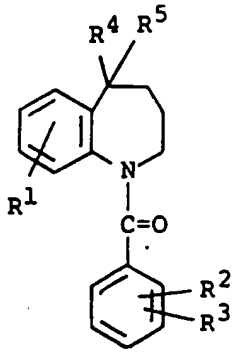
Isomer B: Colorless amorphous

Rf value: 0.4 (developer; ethyl acetate:methanol = 10:1)
^{1}H-NMR ($CDCl_3$) δ ; 1.48 - 2.88, 3.45 - 4.09 (total 21H, m), 4.60 - 5.05 (1H, m), 5.85 - 6.31 (1H, m), 6.62 - 7.78 (10H, m), 7.92 - 8.41 (1H, m)
$[\alpha]_D^{24}$: -107° (methanol, c = 0.2) (measured as hydrochloride)

Examples 90 - 203

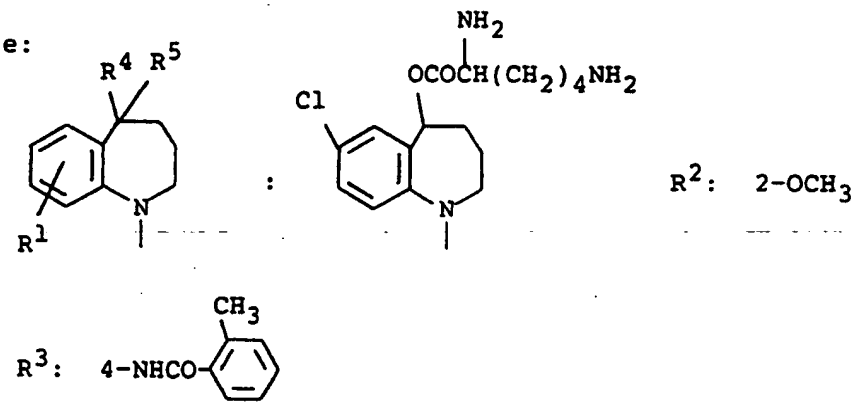
Using the appropriate starting compounds, the compounds of Table 2 are obtained in the same manner as in Examples 1 and 2.

Table 2



Example 90

Structure:



R^2: 2-OCH_3

R^3: 4-NHCO-

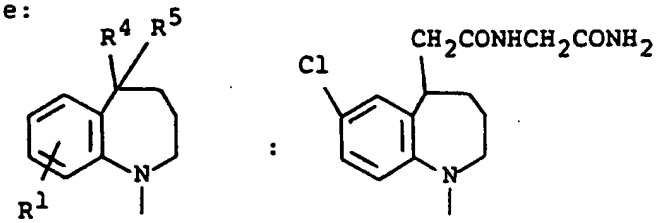
Crystalline form: Colorless amorphous

Form: Dihydrochloride

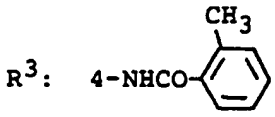
NMR analysis: 46)

Example 91

Structure:



R^2: 2-CH_3



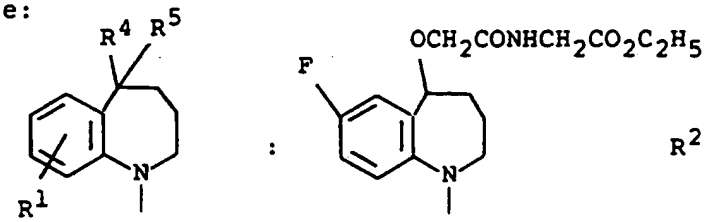
Crystalline form: Colorless amorphous

Form: Free

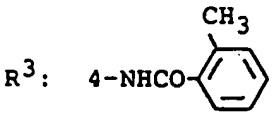
NMR analysis: 144)

Example 92

Structure:



R^2: 2-Cl



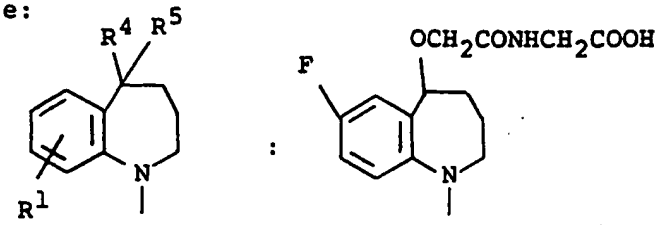
Crystalline form: Colorless amorphous

Form: Free

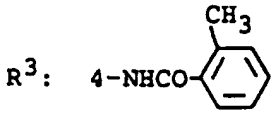
NMR analysis: 47)

Example 93

Structure:



R^2: 2-Cl



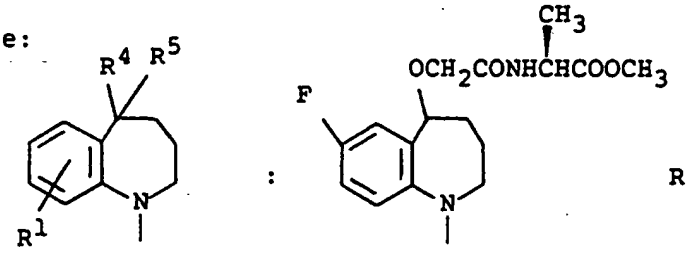
Crystalline form: Colorless amorphous

Form: Free

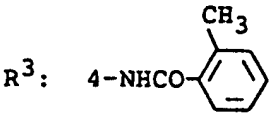
NMR analysis: 48)

Example 94

Structure:



R^2: 2-Cl



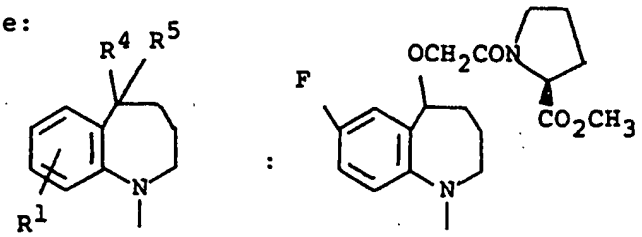
Crystalline form: Colorless amorphous

Form: Free

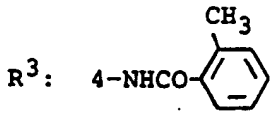
NMR analysis: 49)

Example 95

Structure:



R^2: 2-Cl



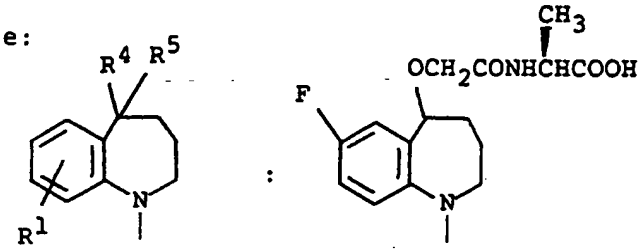
Crystalline form: Slightly yellow amorphous

Form: Free

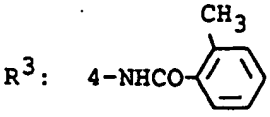
NMR analysis: 50)

Example 96

Structure:



R^2: 2-Cl



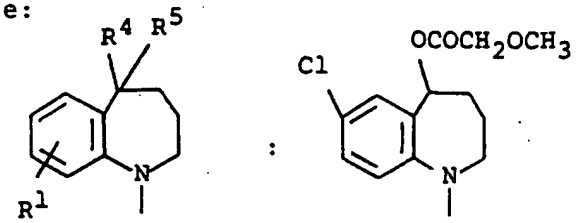
Crystalline form: Slightly yellow amorphous

Form: Free

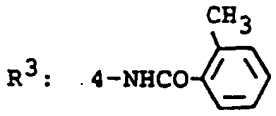
NMR analysis: 51)

Example 97

Structure:



R^2: H



Crystalline form: White powder

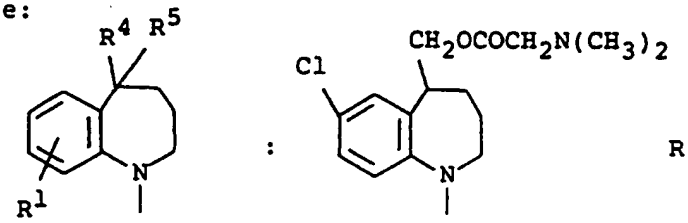
Recrystallization solvent: Dichloromethane/diethyl ether

Melting point: 149 - 152°C

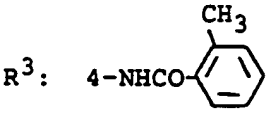
Form: Free

Example 98

Structure:



R^2: H



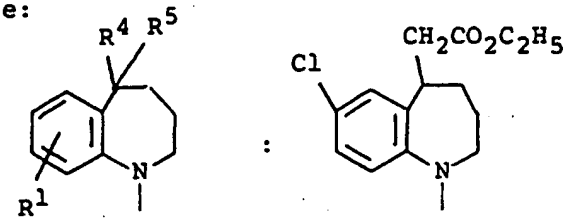
Crystalline form: Colorless amorphous

Form: Hydrochloride

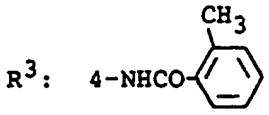
NMR analysis: 96)

Example 99

Structure:



R^2: 3-OCH_3



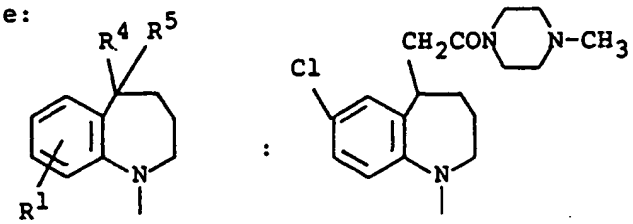
Crystalline form: Colorless amorphous

Form: Free

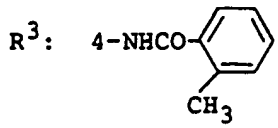
NMR analysis: 52)

Example 100

Structure:



R^2: 3-OCH_3



Crystalline form: Colorless needles

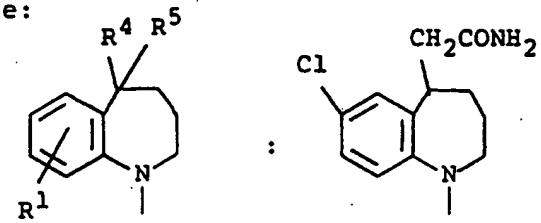
Recrystallization solvent: Ethanol/diethyl ether/n-hexane

Melting point: 182 - 184°C

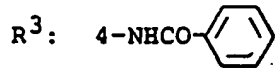
Form: Free

Example 101

Structure:



R^2: 3-OCH_3



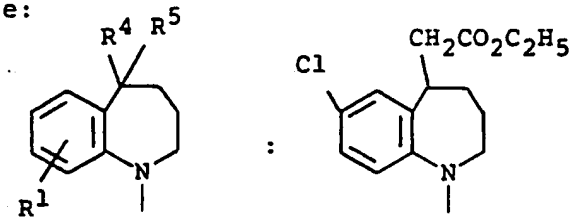
Crystalline form: Colorless amorphous

Form: Free

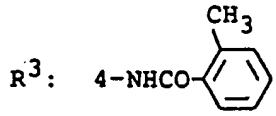
NMR analysis: 53)

Example 102

Structure:



R^2: 2-OCH_3



Crystalline form: Colorless prisms

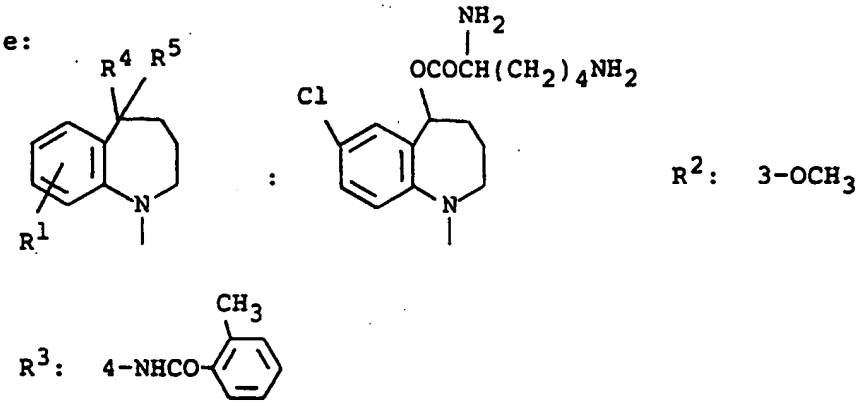
Recrystallization solvent: Ethanol

Melting point: 191 - 193°C

Form: Free

Example 103

Structure:



R^2: 3-OCH_3

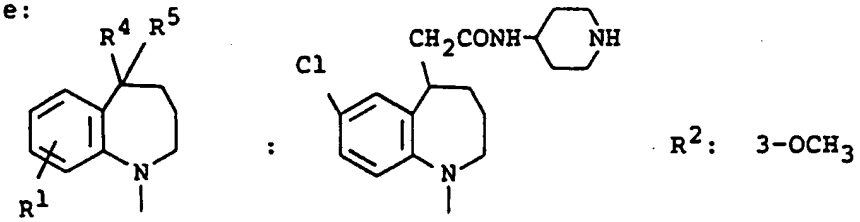
Crystalline form: Colorless amorphous

Form: Dihydrochloride

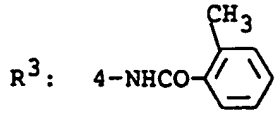
NMR analysis: 131)

Example 104

Structure:



R^2: 3-OCH_3



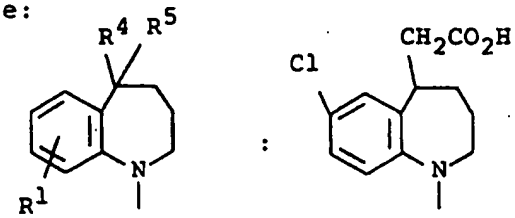
Crystalline form: Colorless amorphous

Form: Hydrochloride

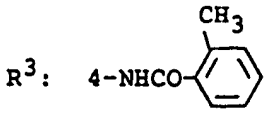
NMR analysis: 54)

Example 105

Structure:



R^2: 2-OCH_3



Crystalline form: White powder

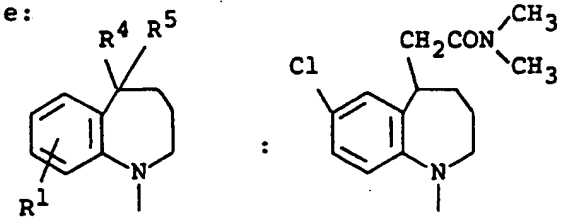
Recrystallization solvent: Ethyl acetate

Melting point: 243.5 - 244.5°C

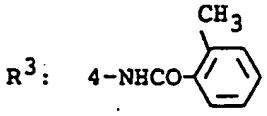
Form: Free

Example 106

Structure:



R^2: 3-OCH_3



Crystalline form: Colorless needles

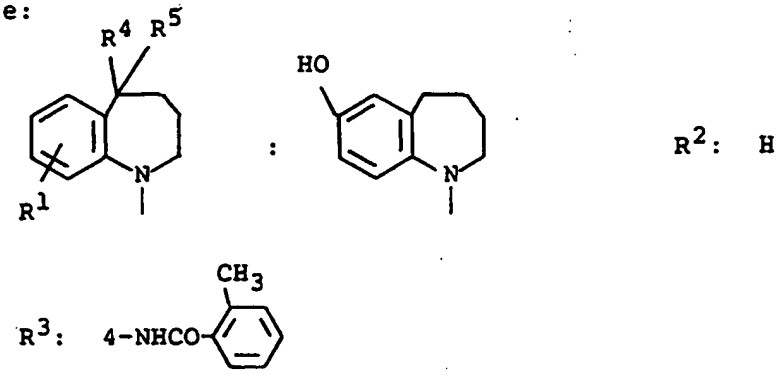
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 164 - 166°C

Form: Free

Example 107

Structure:



R^2: H

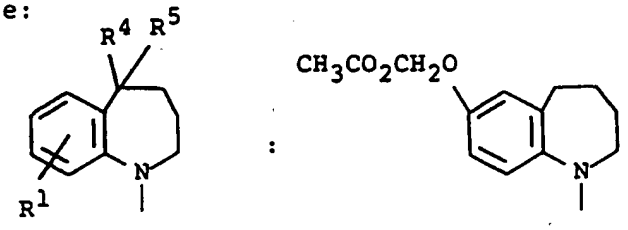
Crystalline form: Colorless prisms

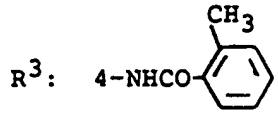
Form: Free

NMR analysis: 132)

Example 108

Structure:





R^2: H

Crystalline form: Colorless needles

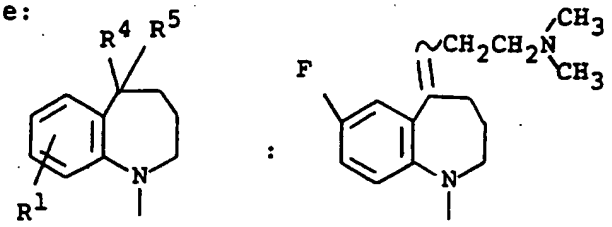
Recrystallization solvent: Methanol/diethyl ether

Melting point: 141 - 144°C

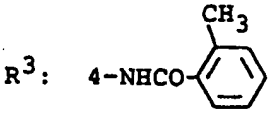
Form: Free

Example 109

Structure:



R^2: 2-Cl



R^3: 4-NHCO-

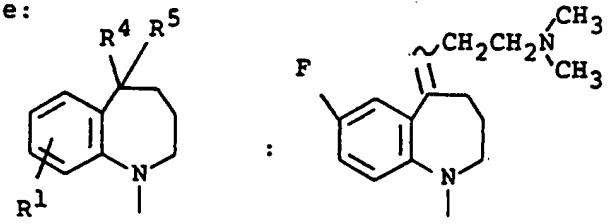
Crystalline form: Yellow amorphous

Form: Hydrochloride

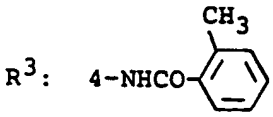
NMR analysis: 55)

Example 110

Structure:



R^2: 2-Cl



R^3: 4-NHCO-

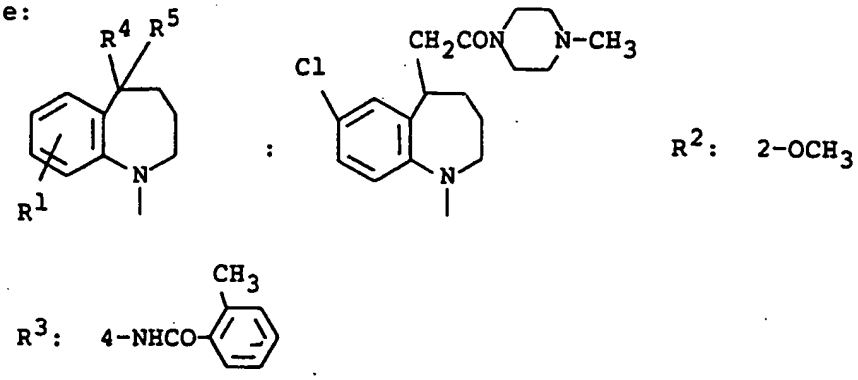
Crystalline form: Yellow amorphous

Form: Hydrochloride

NMR analysis: 56)

Example 111

Structure:



R^2: 2-OCH_3

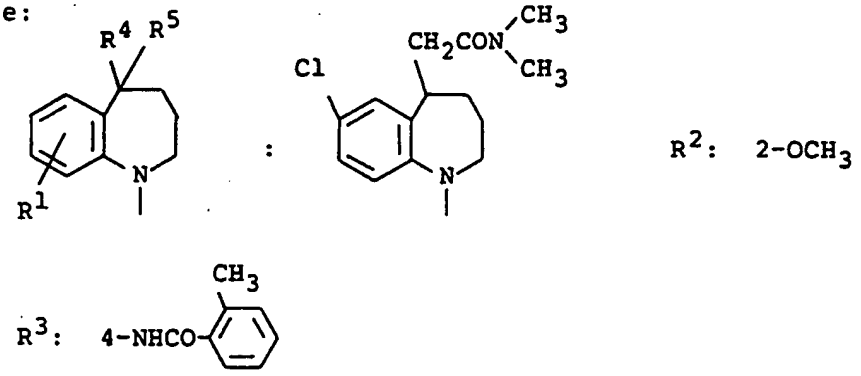
Crystalline form: Colorless amorphous

Form: Hydrochloride

NMR analysis: 57)

Example 112

Structure:



R^2: 2-OCH_3

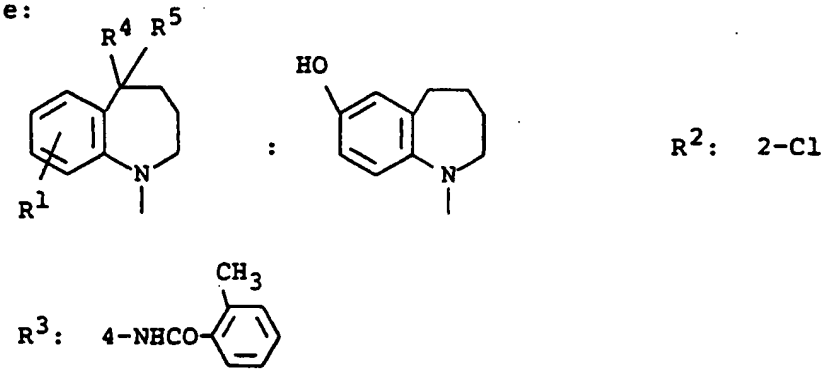
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 58)

Example 113

Structure:



R^2: 2-Cl

R^3: 4-NHCO-(2-CH_3)

Crystalline form: White powder

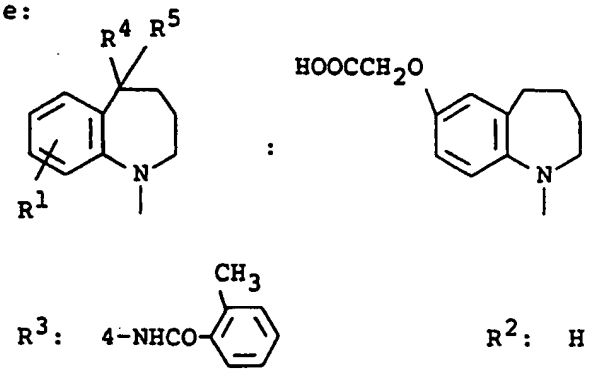
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 254 - 258°C

Form: Free

Example 114

Structure:



R^3: 4-NHCO-(2-CH_3)

R^2: H

Crystalline form: White powder

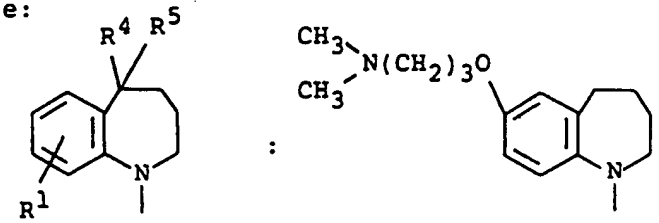
Recrystallization solvent: Ethanol

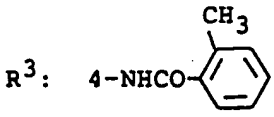
Melting point: 258 - 261°C

Form: Free

Example 115

Structure:





R^2: H

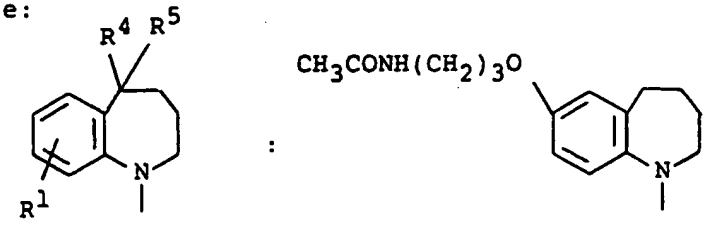
Crystalline form: Colorless amorphous

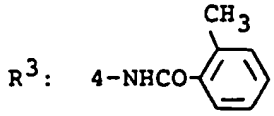
Form: Free

NMR analysis: 133)

Example 116

Structure:





R^2: H

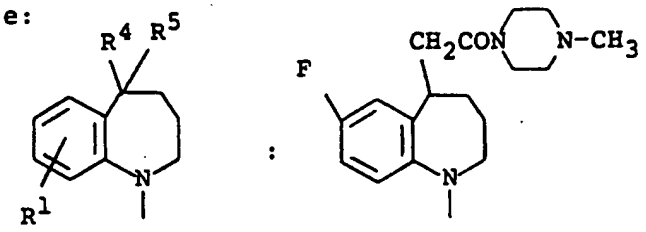
Crystalline form: Colorless amorphous

Form: Free

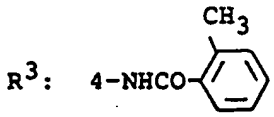
NMR analysis: 134)

Example 117

Structure:



R^2: 2-CH_3



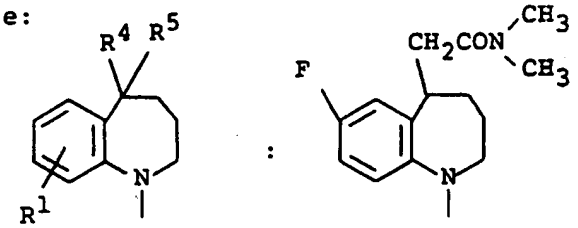
Crystalline form: Colorless amorphous

Form: Free

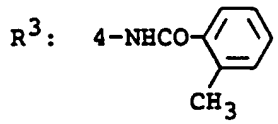
NMR analysis: 108)

Example 118

Structure:



R^2: 2-CH_3



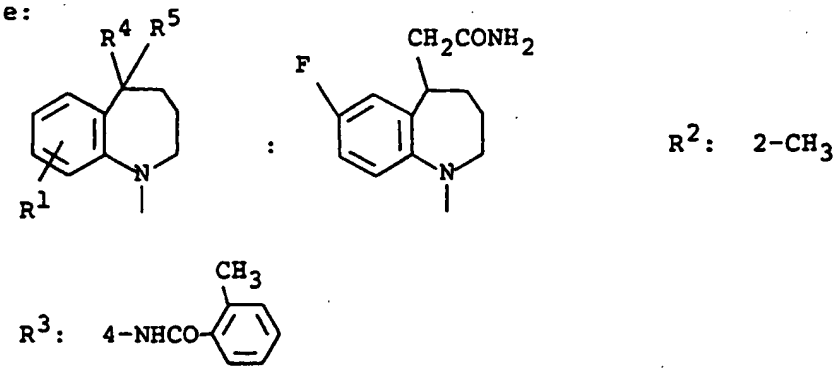
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 109)

Example 119

Structure:



R^2: 2-CH_3

R^3: 4-NHCO-(2-CH_3)

Crystalline form: White powder

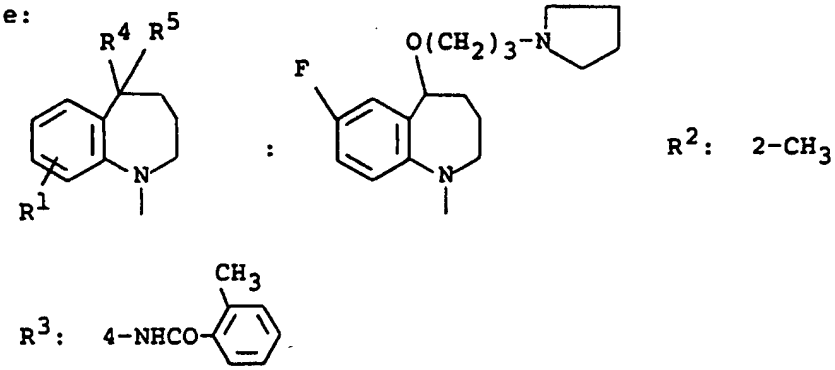
Recrystallization solvent: Ethanol/water

Melting point: 260 - 263°C (decomposed)

Form: Free

Example 120

Structure:



R^2: 2-CH_3

R^3: 4-NHCO-(2-CH_3)

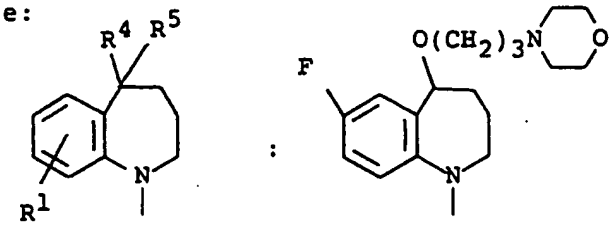
Crystalline form: Colorless amorphous

Form: Free

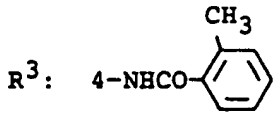
NMR analysis: 110)

Example 121

Structure:



R^2: 2-CH_3



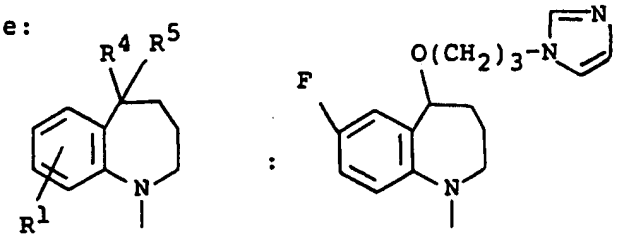
Crystalline form: Colorless amorphous

Form: Free

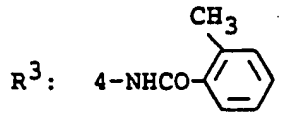
NMR analysis: 111)

Example 122

Structure:



R^2: 2-CH_3



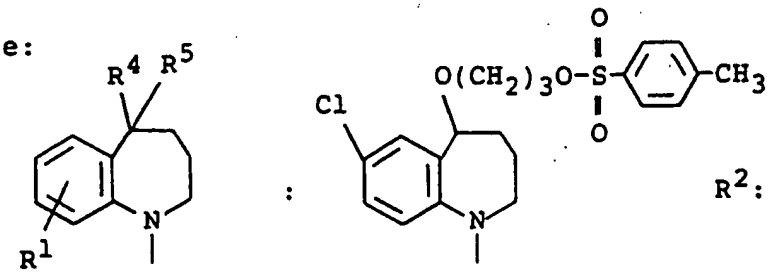
Crystalline form: Colorless amorphous

Form: Free

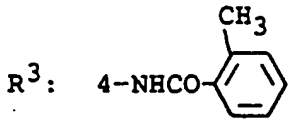
NMR analysis: 112)

Example 123

Structure:



R^2: 2-OCH_3



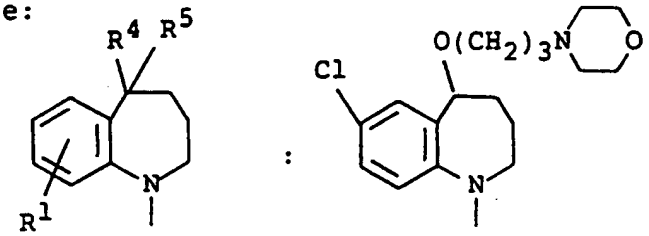
Crystalline form: Colorless amorphous

Form: Free

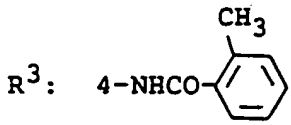
NMR analysis: 59)

Example 124

Structure:



R^2: 2-OCH_3



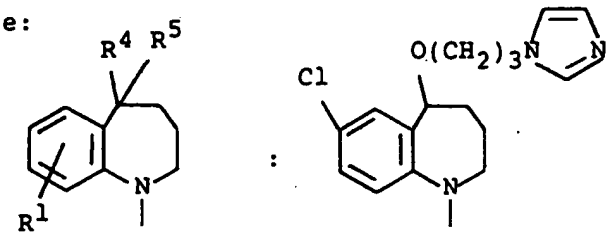
Crystalline form: Pale yellow amorphous

Form: Hydrochloride

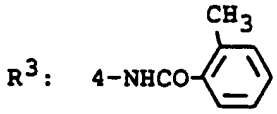
NMR analysis: 60)

Example 125

Structure:



R^2: 2-OCH_3



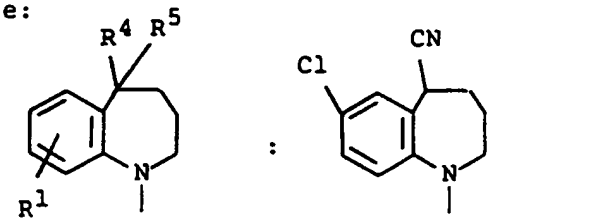
Crystalline form: Colorless amorphous

Form: Hydrochloride

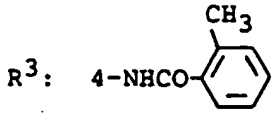
NMR analysis: 61)

Example 126

Structure:



R^2: 3-Cl



Crystalline form: Colorless prisms

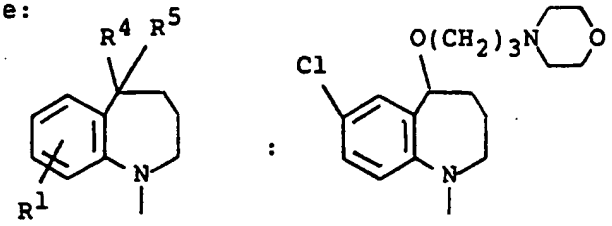
Recrystallization solvent: Ethanol/dichloro methane

Melting point: 213 - 215.5°C

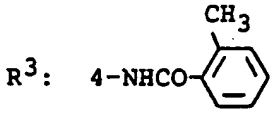
Form: Free

Example 127

Structure:



R^2: 2-CH_3



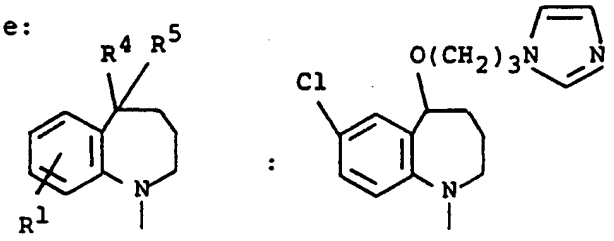
Crystalline form: Colorless amorphous

Form: Hydrochloride

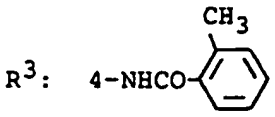
NMR analysis: 62)

Example 128

Structure:



R^2: 2-CH_3



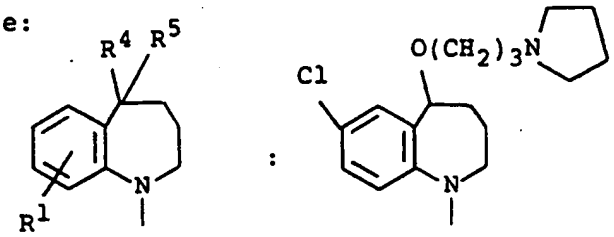
Crystalline form: Colorless amorphous

Form: Dihydrochloride

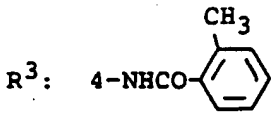
NMR analysis: 63)

Example 129

Structure:



R^2: 2-OCH_3



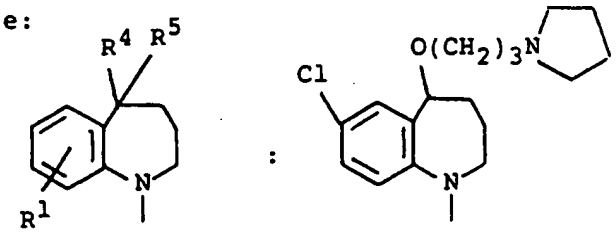
Crystalline form: Pale yellow amorphous

Form: Hydrochloride

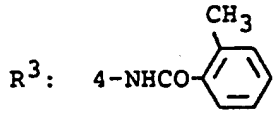
NMR analysis: 64)

Example 130

Structure:



R^2: 2-CH_3



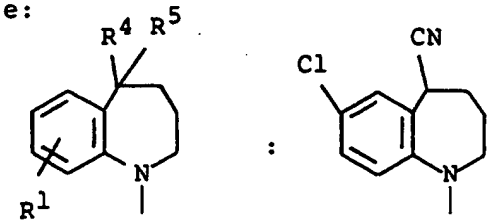
Crystalline form: Slightly yellow amorphous

Form: Hydrochloride

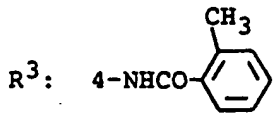
NMR analysis: 65)

Example 131

Structure:



R^2: 2-CH_3



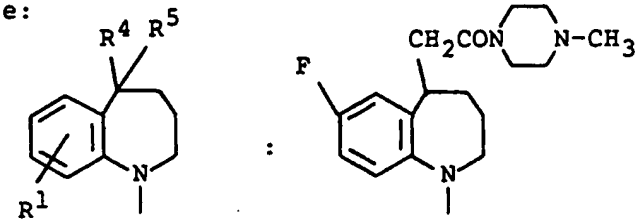
Crystalline form: Colorless amorphous

Form: Free

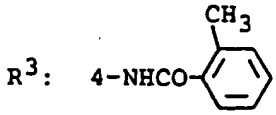
NMR analysis: 66)

Example 132

Structure:



R^2: 2-OCH_3



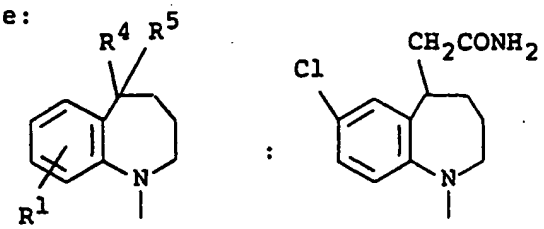
Crystalline form: Colorless amorphous

Form: Free

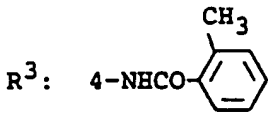
NMR analysis: 116)

Example 133

Structure:



R^2: 2-OCH_3



Crystalline form: Colorless needles

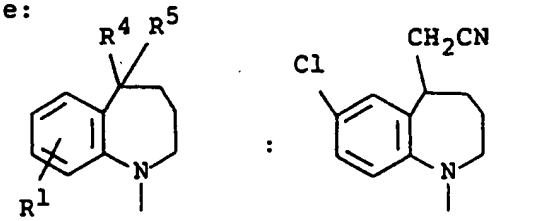
Recrystallization solvent: - Dichloromethane/methanol

Melting point: 202.5 - 203.5°C

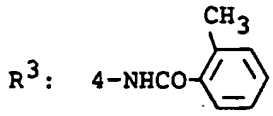
Form: Free

Example 134

Structure:



R^2: 3-OCH_3



Crystalline form: Colorless needles

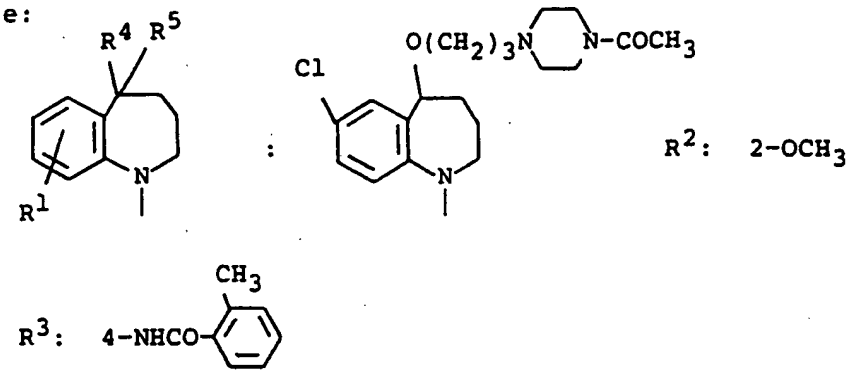
Recrystallization solvent: Ethyl acetate/diethyl ether

Melting point: 164 - 167°C

Form: Free

Example 135

Structure:



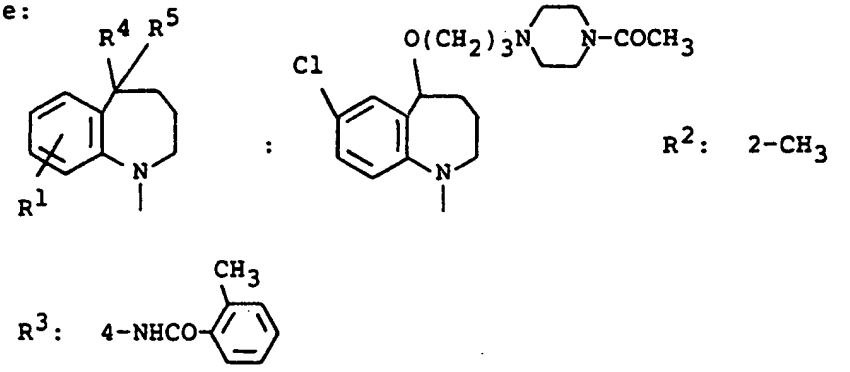
Crystalline form: Pale yellow amorphous

Form: Hydrochloride

NMR analysis: 67)

Example 136

Structure:



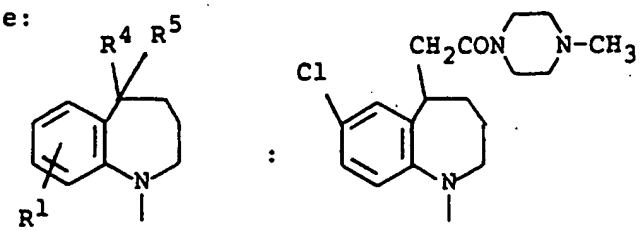
Crystalline form: Colorless amorphous

Form: Hydrochloride

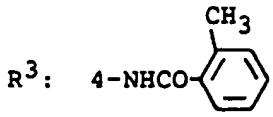
NMR analysis: 68)

Example 137

Structure:



R^2: 2-CH_3



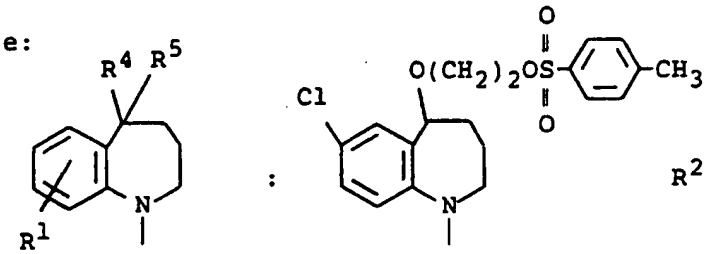
Crystalline form: Colorless amorphous

Form: Hydrochloride

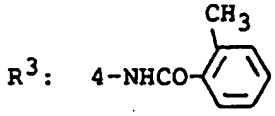
NMR analysis: 69)

Example 138

Structure:



R^2: 2-OCH_3



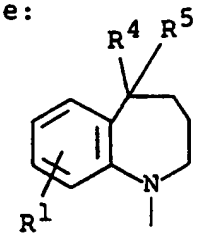
Crystalline form: Colorless amorphous

Form: Free

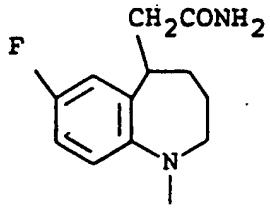
NMR analysis: 70)

Example 139

Structure:

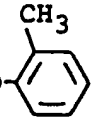


:



R^2: 2-OCH_3

R^3:



Crystalline form: White powder

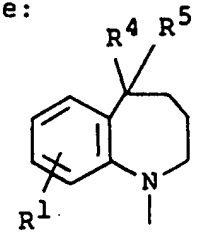
Recrystallization solvent: Ethanol/water

Melting point: 260 - 261°C

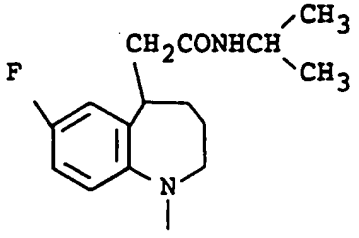
Form: Free

Example 140

Structure:

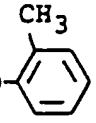


:



R^2: 2-OCH_3

R^3:



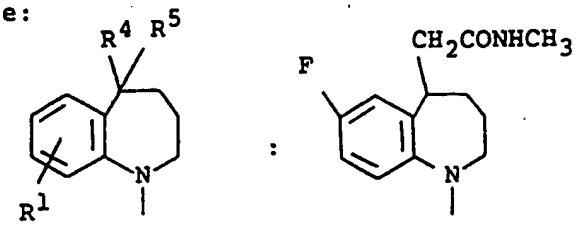
Crystalline form: Colorless amorphous

Form: Free

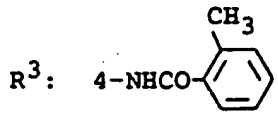
NMR analysis: 113)

Example 141

Structure:



R^2: 2-OCH_3



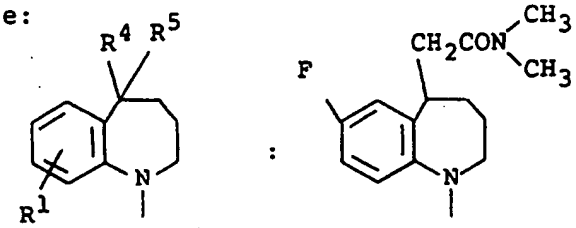
Crystalline form: Colorless amorphous

Form: Free

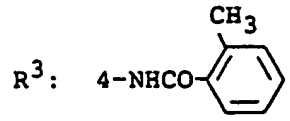
NMR analysis: 114)

Example 142

Structure:



R^2: 2-OCH_3



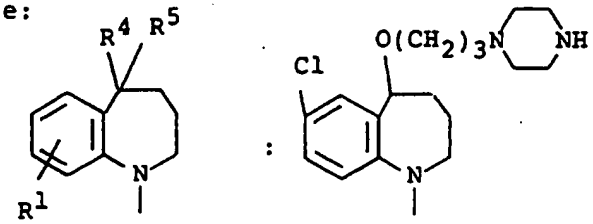
Crystalline form: Colorless amorphous

Form: Free

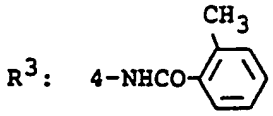
NMR analysis: 115)

Example 143

Structure:



R^2: 2-OCH_3



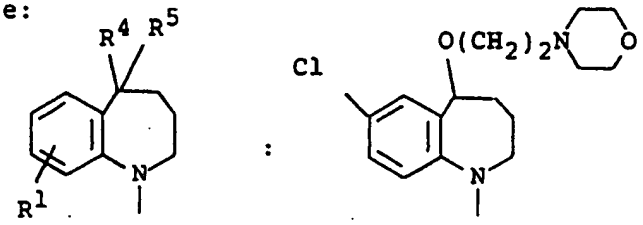
Crystalline form: Colorless amorphous

Form: Dihydrochloride

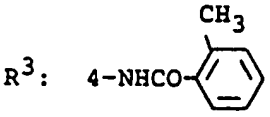
NMR analysis: 71)

Example 144

Structure:



R^2: 2-OCH_3



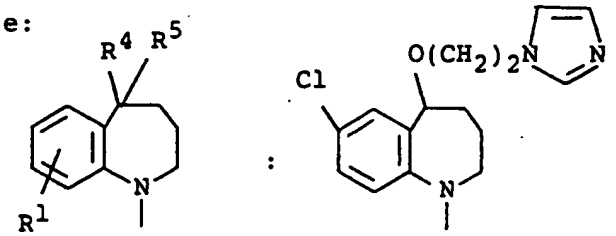
Crystalline form: Colorless amorphous

Form: Hydrochloride

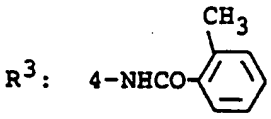
NMR analysis: 72)

Example 145

Structure:



R^2: 2-OCH_3



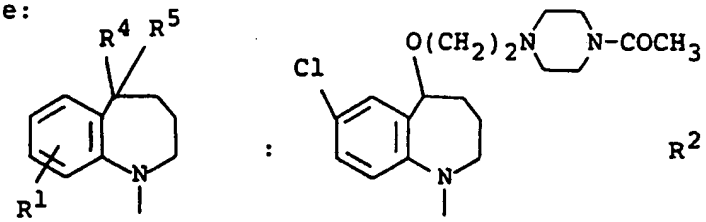
Crystalline form: Colorless amorphous

Form: Hydrochloride

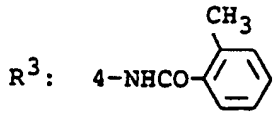
NMR analysis: 73)

Example 146

Structure:



R^2: 2-OCH_3



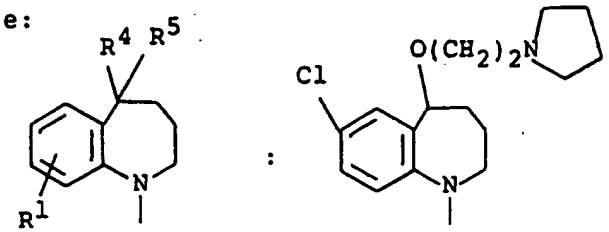
Crystalline form: Pale yellow amorphous

Form: Hydrochloride

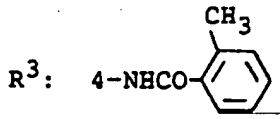
NMR analysis: 74)

Example 147

Structure:



R^2: 2-OCH_3



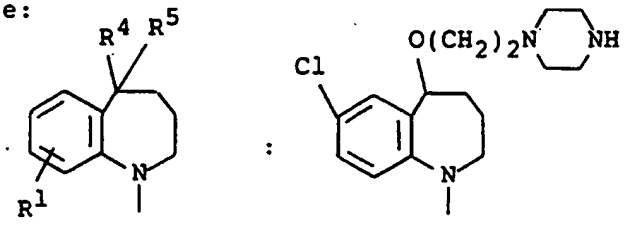
Crystalline form: Pale yellow amorphous

Form: Hydrochloride

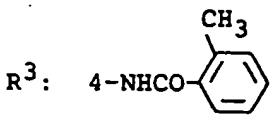
NMR analysis: 75)

Example 148

Structure:



R^2: 2-OCH_3



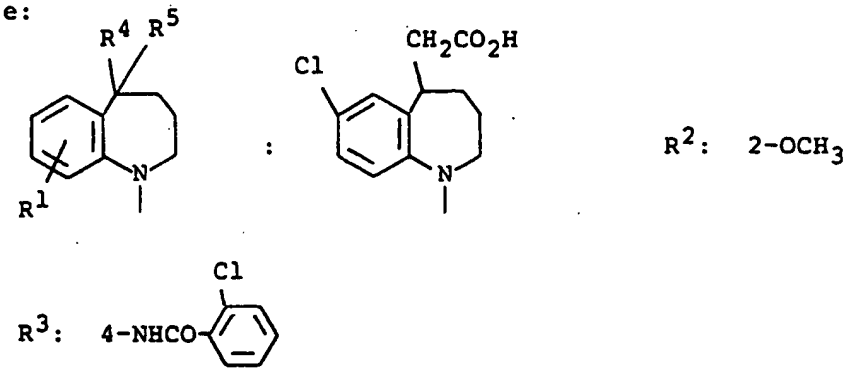
Crystalline form: Colorless amorphous

Form: Dihydrochloride

NMR analysis: 76)

Example 149

Structure:



R^2: 2-OCH_3

Crystalline form: White powder

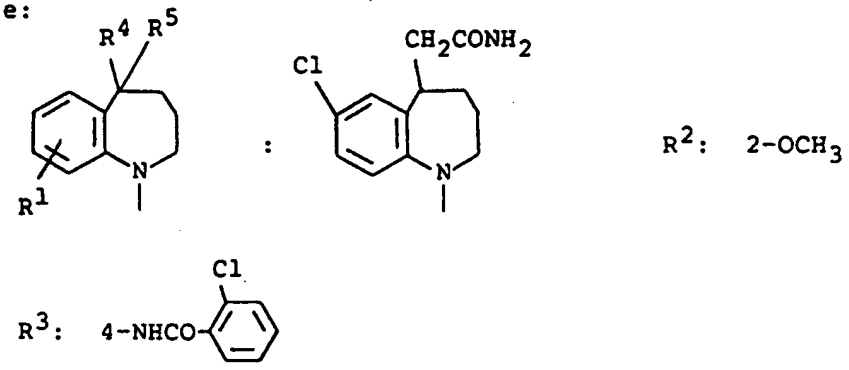
Recrystallization solvent: Dichloromethane/diethyl ether

Melting point: 190 - 193°C

Form: Free

Example 150

Structure:



R^2: 2-OCH_3

Crystalline form: Colorless prisms

Recrystallization solvent: Ethanol/n-hexane

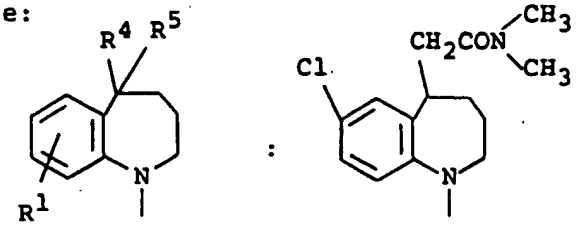
Melting point: 168 - 175°C

Form: Free

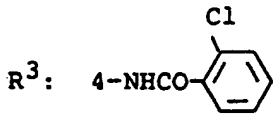
NMR analysis: 146)

Example 151

Structure:



R^2: 2-OCH_3



Crystalline form: Colorless prisms

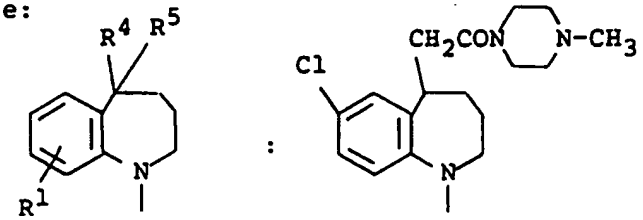
Recrystallization solvent: Ethyl acetate/diethyl ether

Melting point: 153 - 155°C

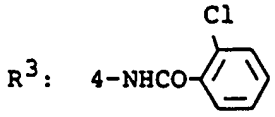
Form: Free

Example 152

Structure:



R^2: 2-OCH_3



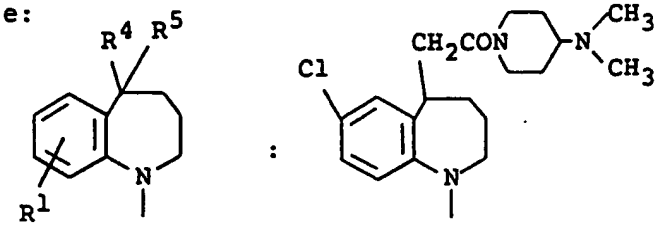
Crystalline form: Colorless amorphous

Form: Hydrochloride

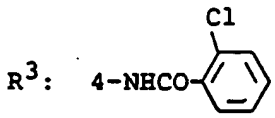
NMR analysis: 77)

Example 153

Structure:



R^2: 2-OCH_3



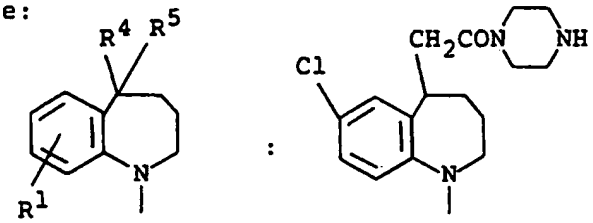
Crystalline form: Colorless amorphous

Form: Hydrochloride

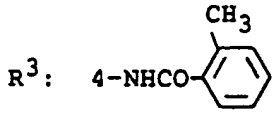
NMR analysis: 78)

Example 154

Structure:



R^2: 2-OCH_3



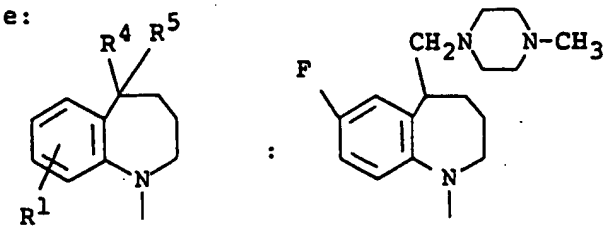
Crystalline form: Colorless amorphous

Form: Hydrochloride

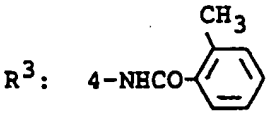
NMR analysis: 79)

Example 155

Structure:



R^2: 2-OCH_3



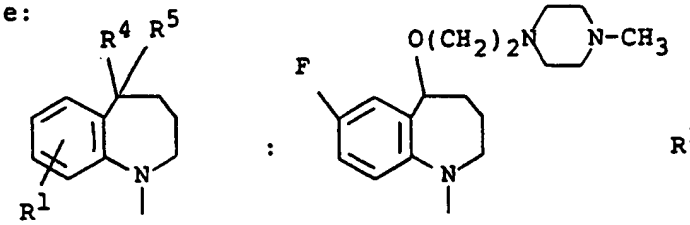
Crystalline form: Colorless amorphous

Form: Free

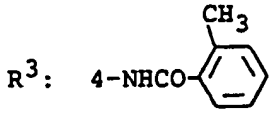
NMR analysis: 117)

Example 156

Structure:



R^2: 2-OCH_3



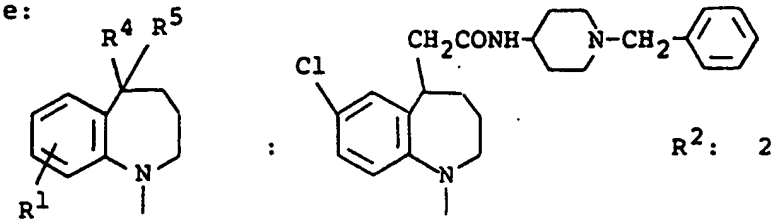
Crystalline form: Colorless amorphous

Form: Free

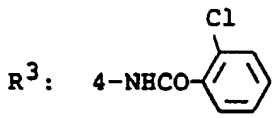
NMR analysis: 118)

Example 157

Structure:



R^2: 2-OCH_3



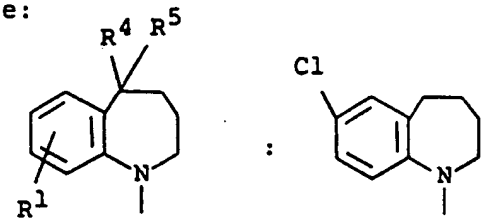
Crystalline form: Colorless amorphous

Form: Hydrochloride

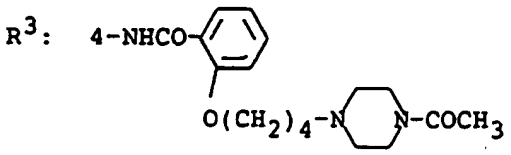
NMR analysis: 80)

Example 158

Structure:



R^2: 2-OCH_3



Crystalline form: Colorless needles

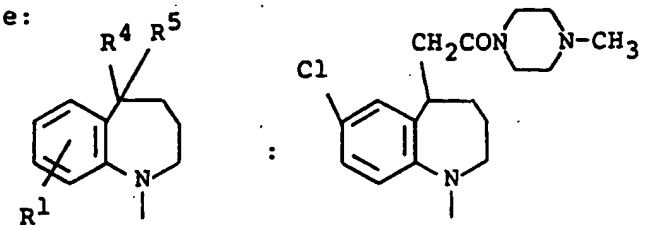
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 99 - 102°C

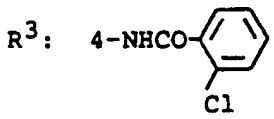
Form: Free

Example 159

Structure:



R^2: 2-CH_3



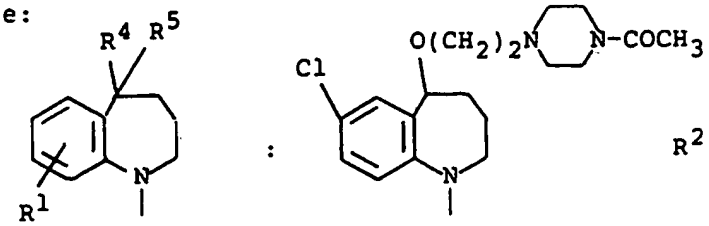
Crystalline form: Colorless amorphous

Form: Hydrochloride

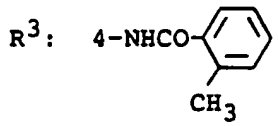
NMR analysis: 81)

Example 160

Structure:



R^2: 2-CH_3



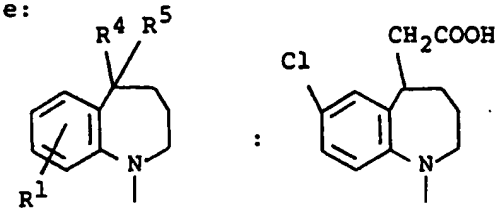
Crystalline form: Slightly yellow amorphous

Form: Hydrochloride

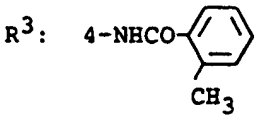
NMR analysis: 82)

Example 161

Structure:



R^2: 2-Cl



Crystalline form: White powder

Recrystallization solvent: Ethyl acetate/diethyl ether

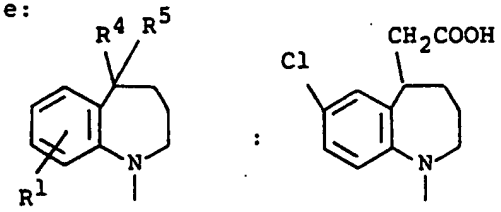
Melting point: 227°C

Form: Free

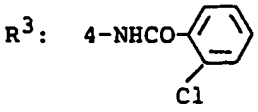
NMR analysis: 102)

Example 162

Structure:



R^2: 2-CH_3



Crystalline form: White powder

Recrystallization solvent: Ethyl acetate/n-hexane

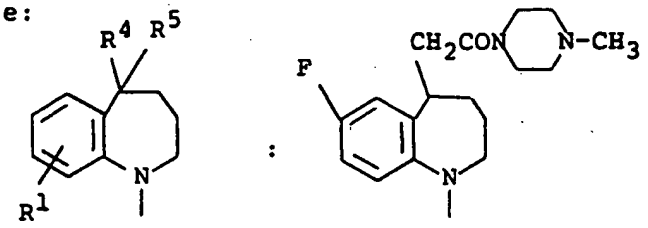
Melting point: 231 - 232°C

Form: Free

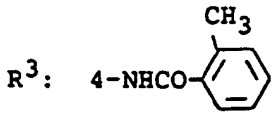
NMR analysis: 101)

Example 163

Structure:



R^2: H



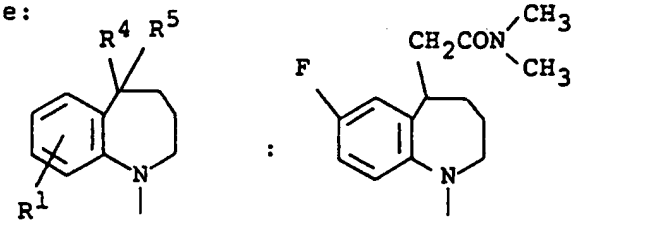
Crystalline form: Colorless amorphous

Form: Free

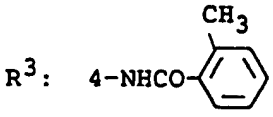
NMR analysis: 119)

Example 164

Structure:



R^2: H



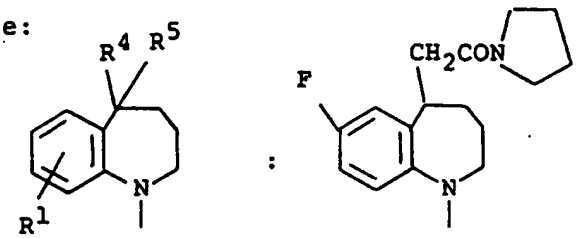
Crystalline form: Colorless amorphous

Form: Free

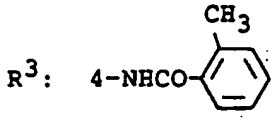
NMR analysis: 120)

Example 165

Structure:



R^2: H



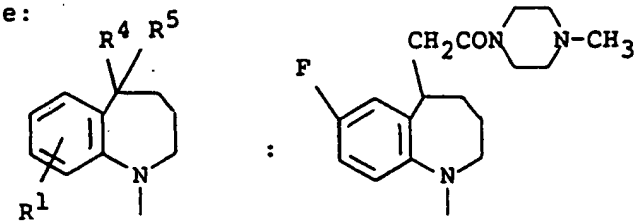
Crystalline form: Colorless amorphous

Form: Free

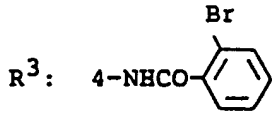
NMR analysis: 121)

Example 166

Structure:



R^2: 2-OCH_3



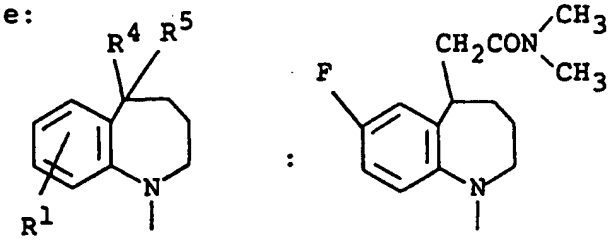
Crystalline form: Colorless amorphous

Form: Free

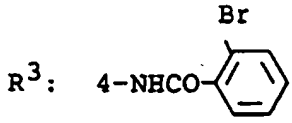
NMR analysis: 122)

Example 167

Structure:



R^2: 2-OCH_3



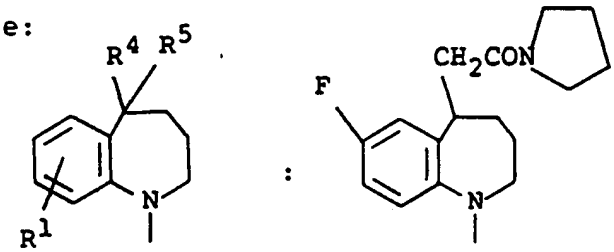
Crystalline form: Colorless amorphous

Form: Free

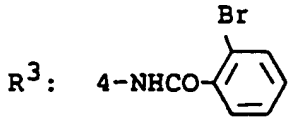
NMR analysis: 123)

Example 168

Structure:



R^2: 2-OCH_3



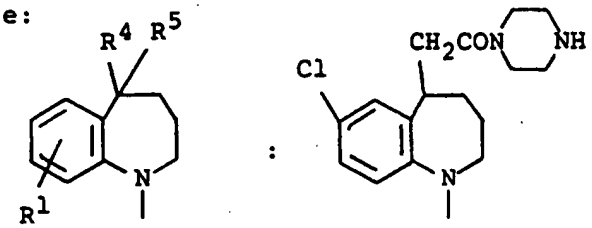
Crystalline form: Colorless amorphous

Form: Free

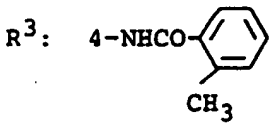
NMR analysis: 124)

Example 169

Structure:



R^2: 2-CH_3



Crystalline form: White powder

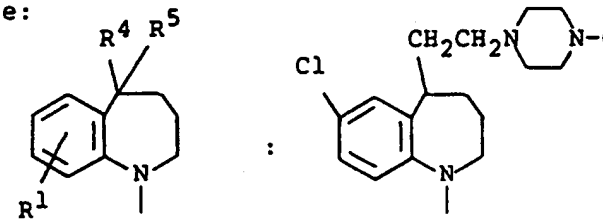
Recrystallization solvent: - Ethanol/diethyl ether

Melting point: 196°C

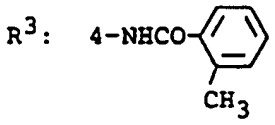
Form: Hydrochloride

Example 170

Structure:



R^2: 2-CH_3



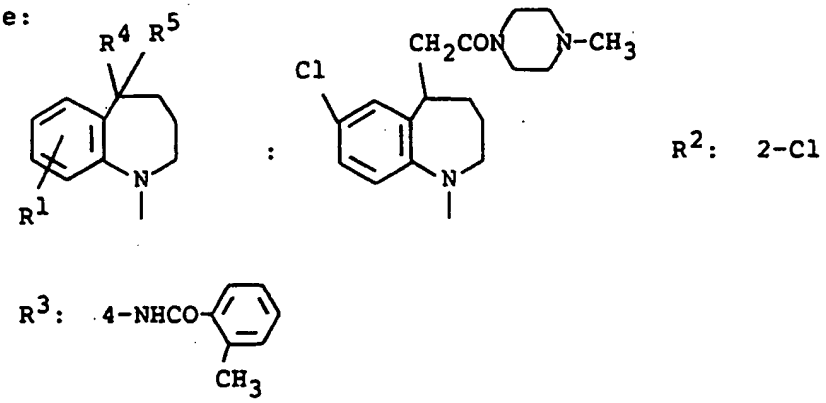
Crystalline form: Colorless amorphous

Form: Hydrochloride

NMR analysis: 83)

Example 171

Structure:



R^2: 2-Cl

R^3: 4-NHCO-(2-CH_3)

Crystalline form: White powder

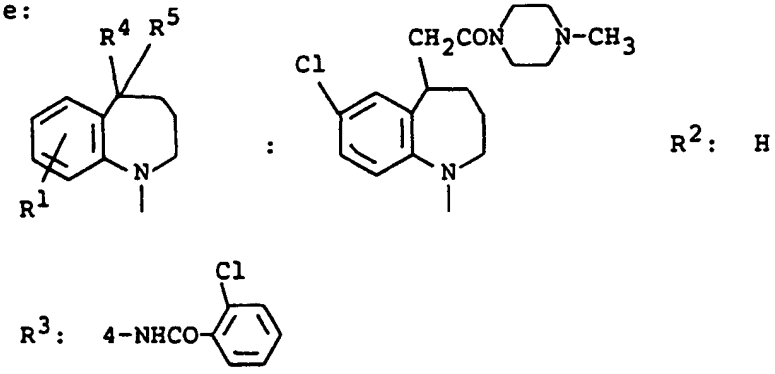
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 182 - 183°C

Form: Hydrochloride

Example 172

Structure:



R^2: H

R^3: 4-NHCO-(2-Cl)

Crystalline form: Colorless prisms

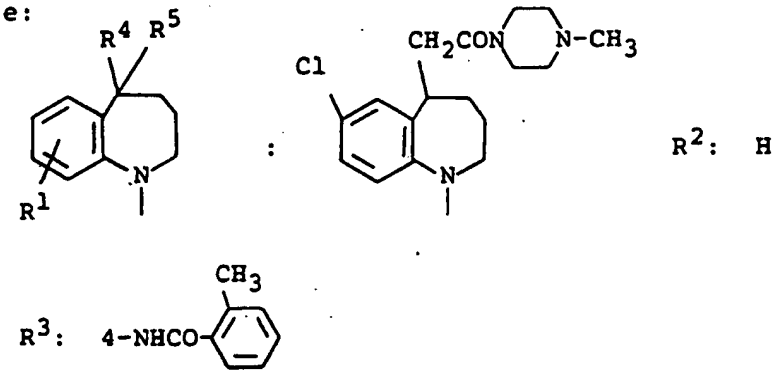
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 193 - 195°C (decomposed)

Form: Hydrochloride

Example 173

Structure:



R^2: H

Crystalline form: Colorless prisms

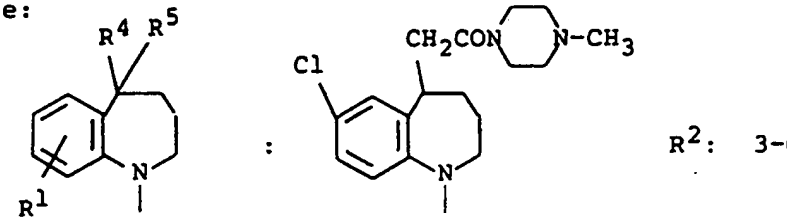
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 190 - 193°C (decomposed)

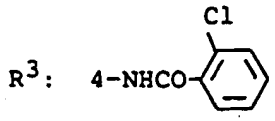
Form: Hydrochloride

Example 174

Structure:



R^2: 3-OCH_3



Crystalline form: White powder

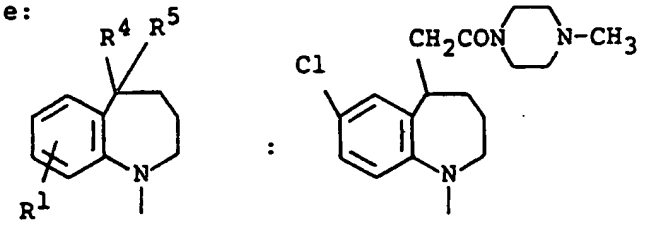
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 208 - 209°C

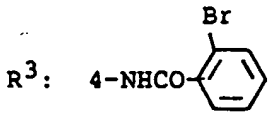
Form: Hydrochloride

Example 175

Structure:



R^2: 3-OCH_3



Crystalline form: White powder

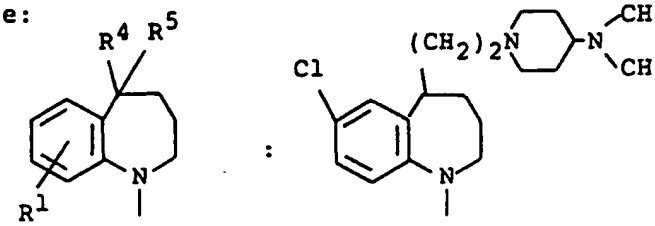
Recrystallization solvent: - Ethanol/acetone/diethyl ether

Melting point: 215 - 217°C

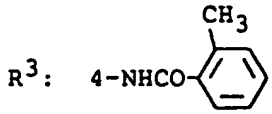
Form: Hydrochloride

Example 176

Structure:



R^2: 2-OCH_3



Crystalline form: Colorless needles

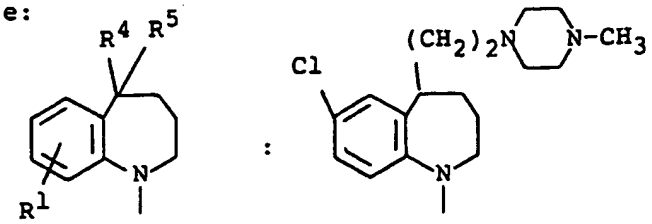
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 222 - 224°C

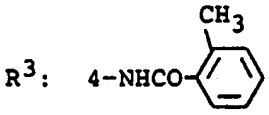
Form: Dihydrochloride

Example 178

Structure:



R^2: 2-OCH_3



Crystalline form: Colorless needles

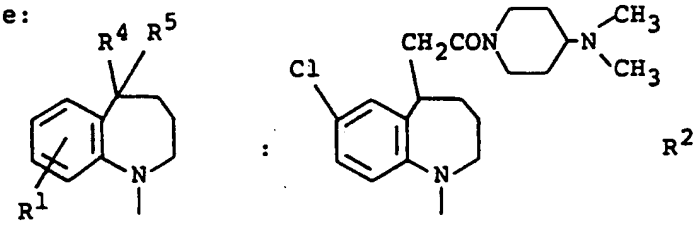
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 214 - 216°C

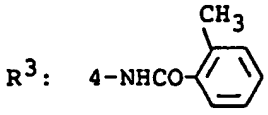
Form: Dihydrochloride

Example 179

Structure:



R^2: 2-CH_3



Crystalline form: White powder

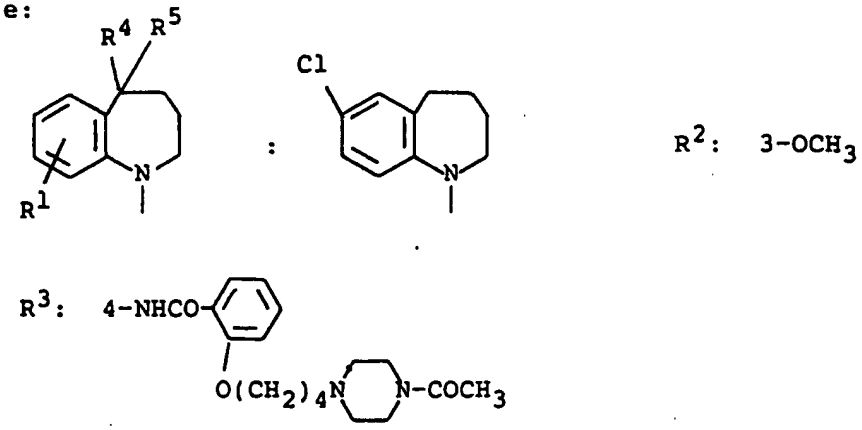
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 254 - 256°C

Form: Hydrochloride

Example 180

Structure:



Crystalline form: Colorless needles

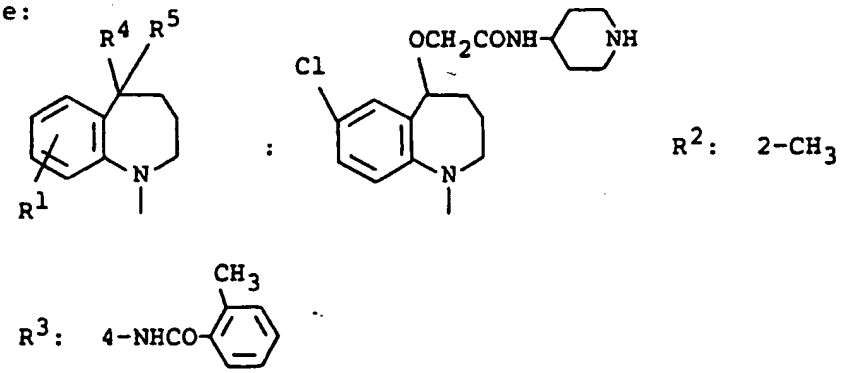
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 148 - 150°C

Form: Free

Example 181

Structure:



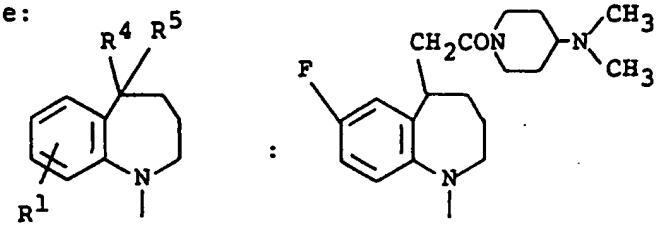
Crystalline form: Colorless amorphous

Form: Hydrochloride

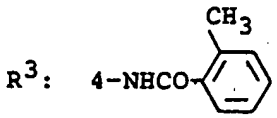
NMR analysis: 145)

Example 182

Structure:



R^2: 2-OCH_3



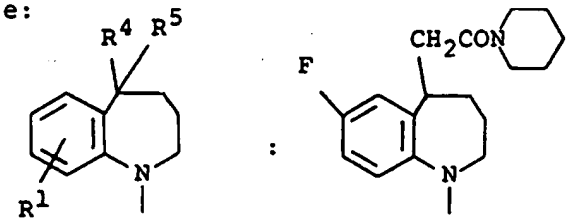
Crystalline form: Colorless amorphous

Form: Free

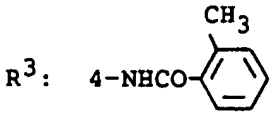
NMR analysis: 125)

Example 183

Structure:



R^2: 2-OCH_3



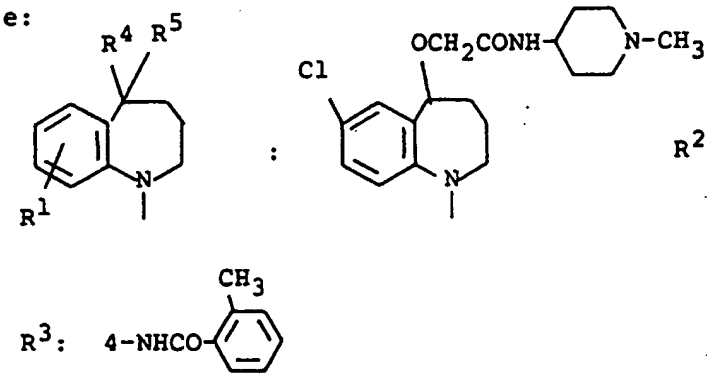
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 126)

Example 184

Structure:



Crystalline form: White powder

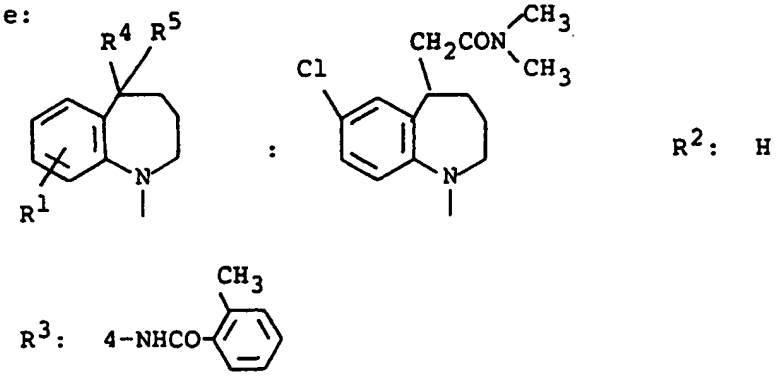
Recrystallization solvent: Ethanol/diethyl ether

Melting point: 186 - 188°C

Form: Hydrochloride

Example 185

Structure:



Crystalline form: White powder

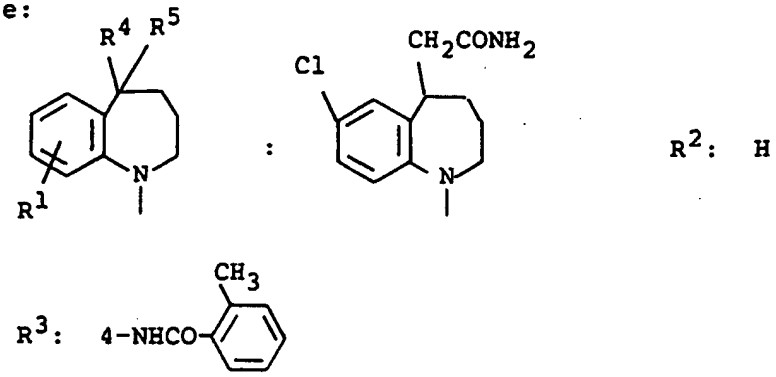
Recrystallization solvent: Dichloromethane/diethyl ether

Melting point: 239.5 - 240.5°C

Form: Free

Example 186

Structure:



Crystalline form: White powder

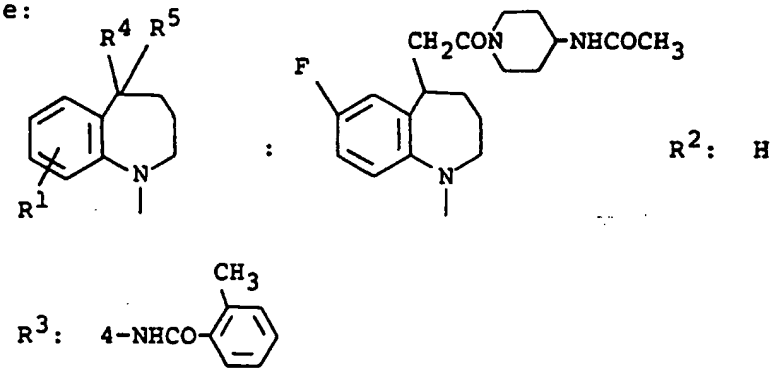
Recrystallization solvent: Dichloromethane/diethyl ether

Melting point: 253 - 255°C

Form: Free

Example 187

Structure:



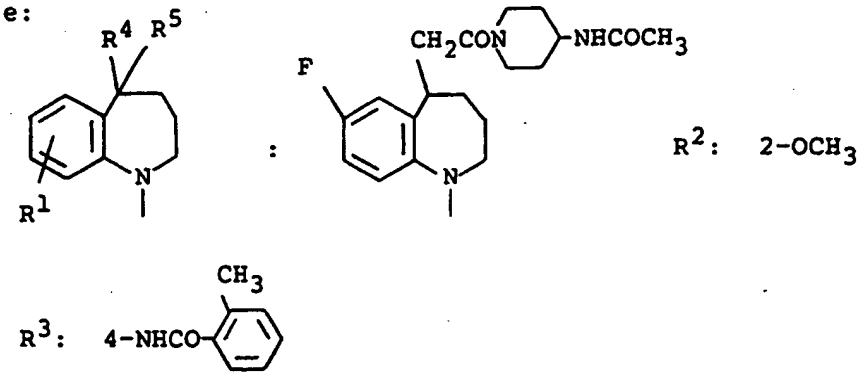
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 127)

Example 188

Structure:



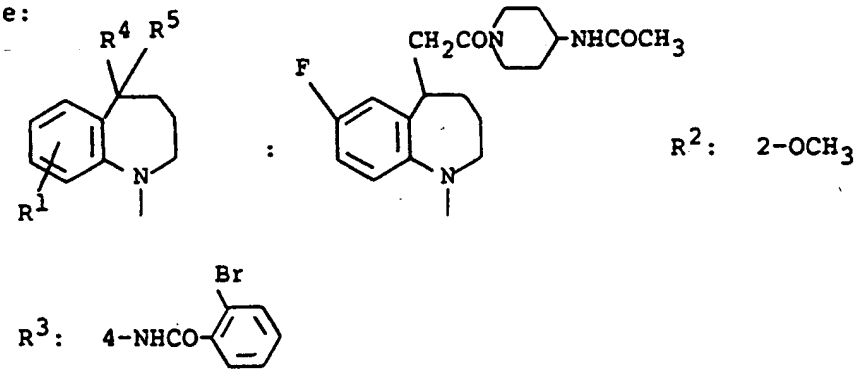
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 128)

Example 189

Structure:



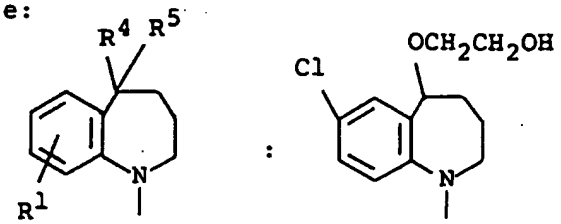
Crystalline form: Colorless amorphous

Form: Free

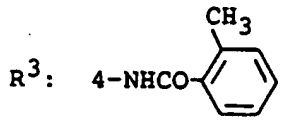
NMR analysis: 129)

Example 190

Structure:



R^2: H



Crystalline form: White powder

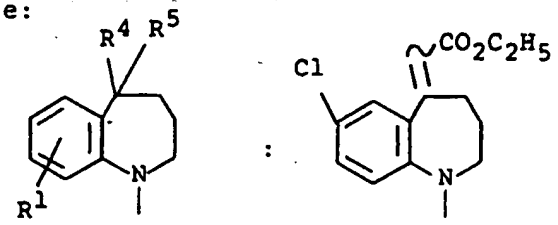
Recrystallization solvent: Dichloromethane/diethyl ether

Melting point: 185 - 187.5°C

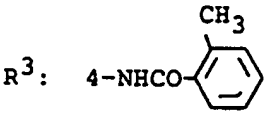
Form: Free

Example 191

Structure:



R^2: 2-OCH_3



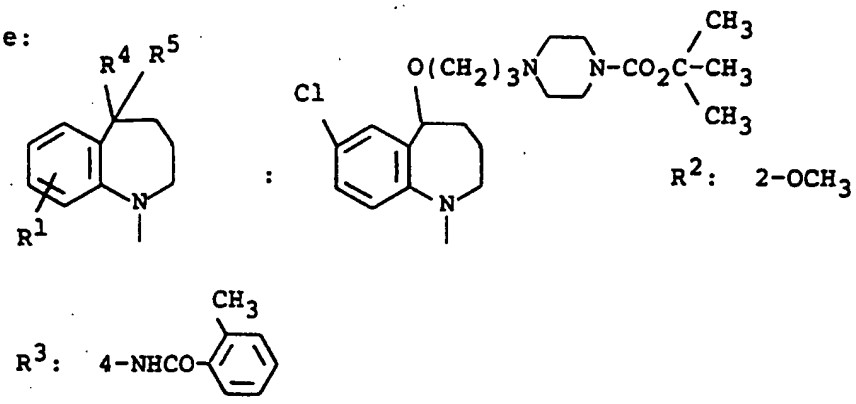
Crystalline form: Pale yellow oil

Form: Free

NMR analysis: 84)

Example 192

Structure:



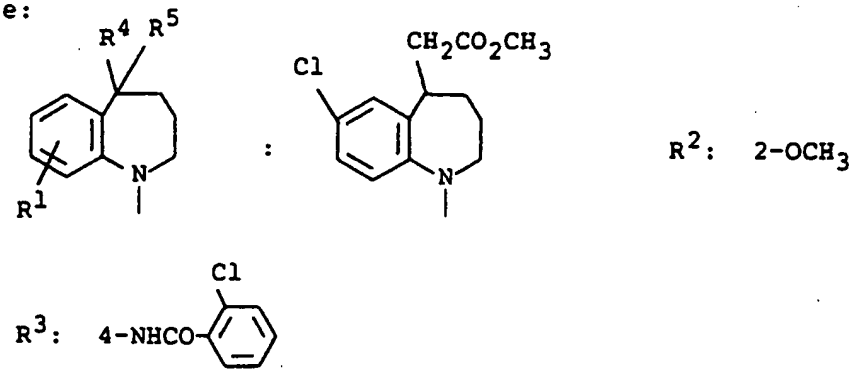
Crystalline form: Pale yellow amorphous

Form: Free

NMR analysis: 85)

Example 193

Structure:



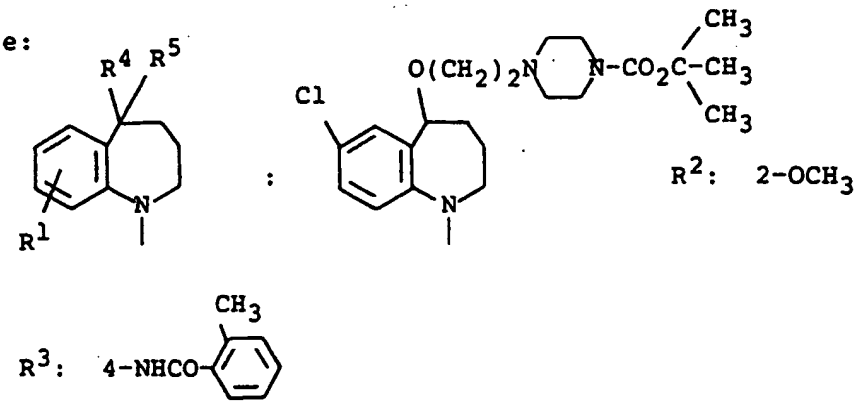
Crystalline form: Pale yellow amorphous

Form: Free

NMR analysis: 86)

Example 194

Structure:



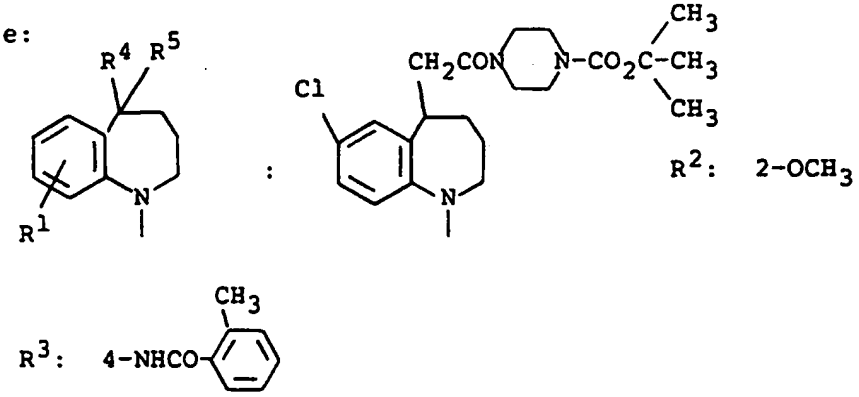
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 87)

Example 195

Structure:



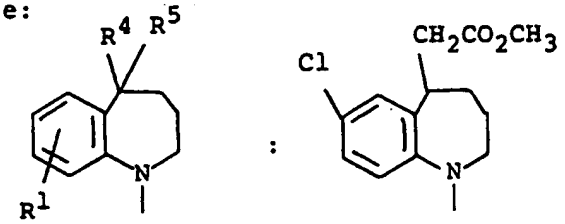
Crystalline form: White powder

Melting point: 145 - 147°C

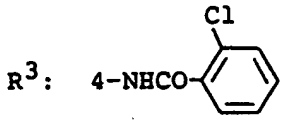
Form: Free

Example 196

Structure:



R^2: H



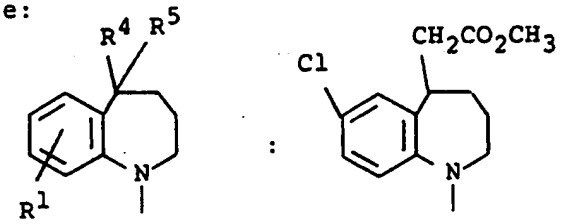
Crystalline form: Colorless amorphous

Form: Free

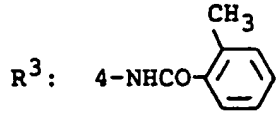
NMR analysis: 88)

Example 197

Structure:



R^2: 2-OCH_3



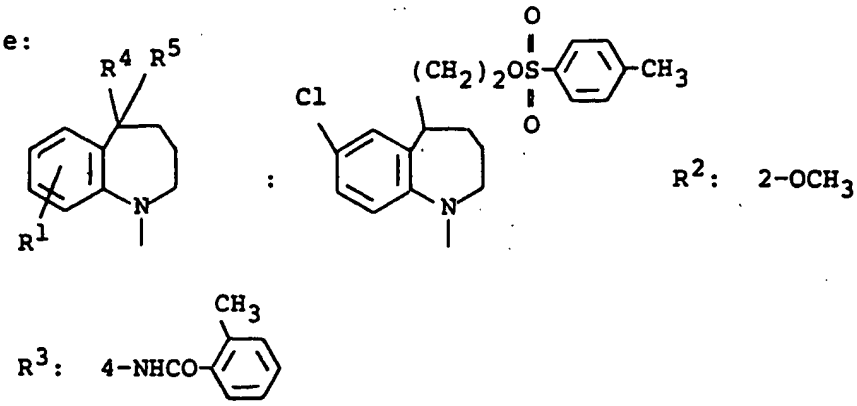
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 89)

Example 198

Structure:



R^2: 2-OCH_3

R^3: 4-NHCO-(2-CH_3)

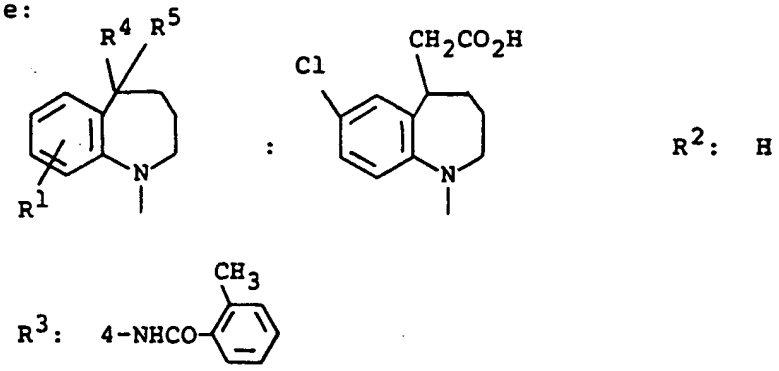
Crystalline form: Pale yellow amorphous

Form: Free

NMR analysis: 90)

Example 199

Structure:



R^2: H

R^3: 4-NHCO-(2-CH_3)

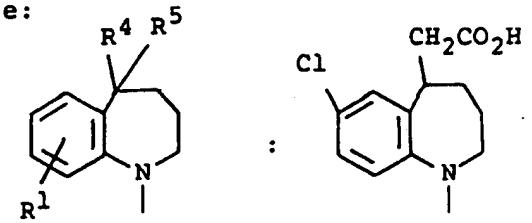
Crystalline form: Colorless amorphous

Form: Free

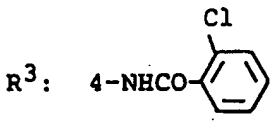
NMR analysis: 91)

Example 200

Structure:



R^2: H



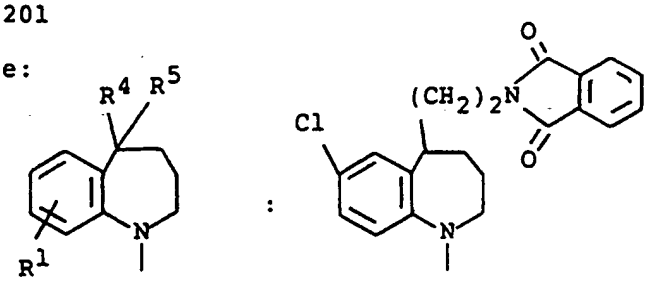
Crystalline form: Colorless amorphous

Form: Free

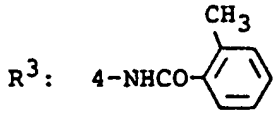
NMR analysis: 92)

Example 201

Structure:



R^2: 2-OCH_3



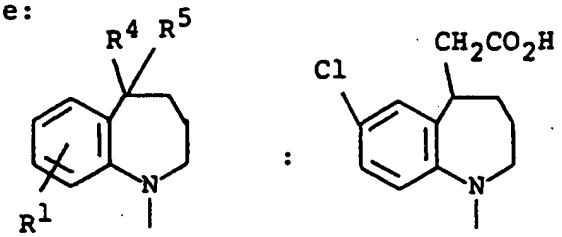
Crystalline form: White powder

Form: Free

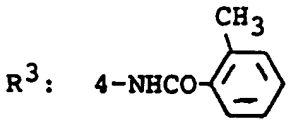
NMR analysis: 93)

Example 202

Structure:



R^2: 3-OCH_3



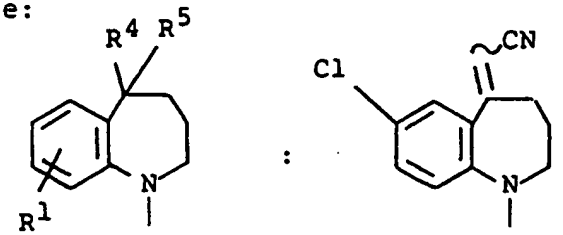
Crystalline form: Colorless amorphous

Form: Free

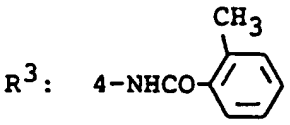
NMR analysis: 94)

Example 203

Structure:



R^2: 3-OCH_3



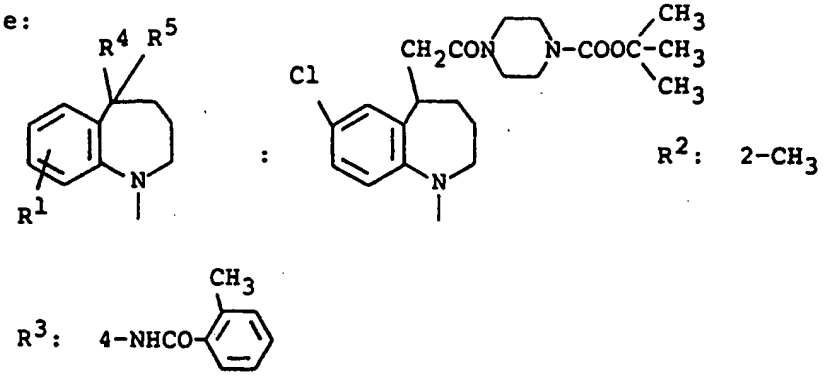
Crystalline form: Colorless powder

Form: Free

NMR analysis: 95)

Example 204

Structure:



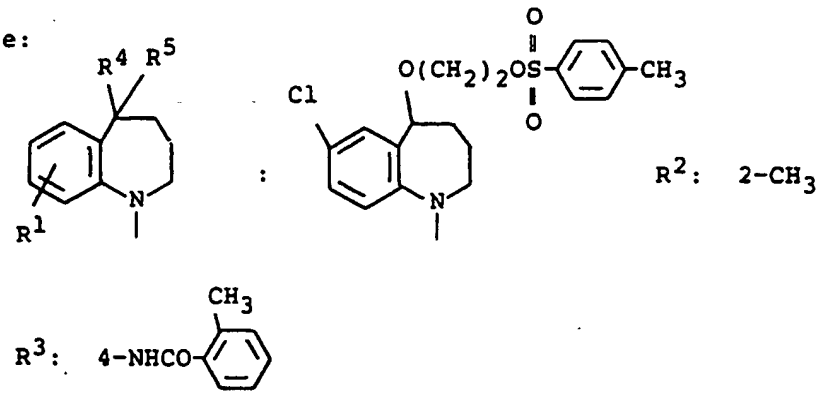
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 97)

Example 205

Structure:



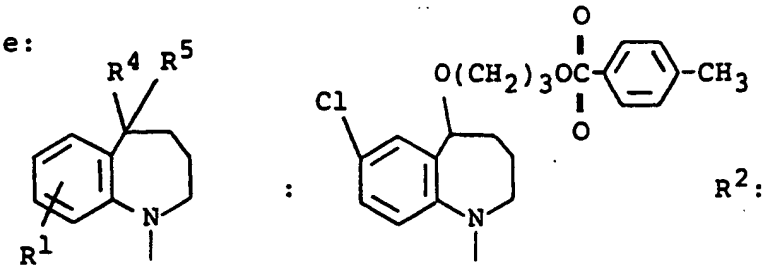
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 98)

Example 206

Structure:



R^2: 2-CH_3

R^3: 4-NHCO- (2-CH_3)

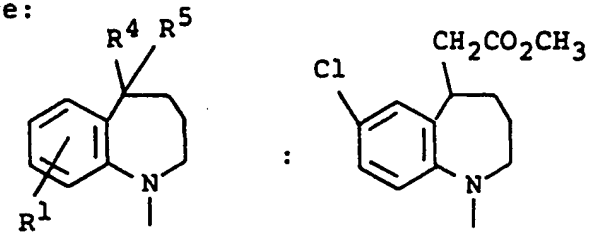
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 99)

Example 207

Structure:



R^2: 2-CH_3

R^3: 4-NHCO- (2-Cl)

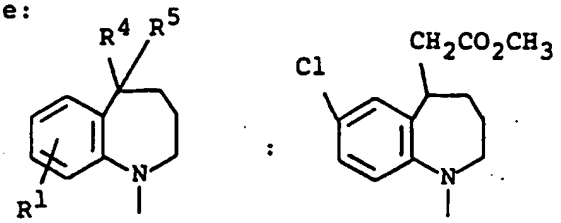
Crystalline form: Colorless amorphous

Form: Free

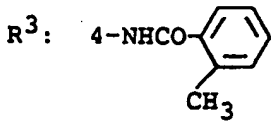
NMR analysis: 100)

Example 208

Structure:



R^2: 2-Cl



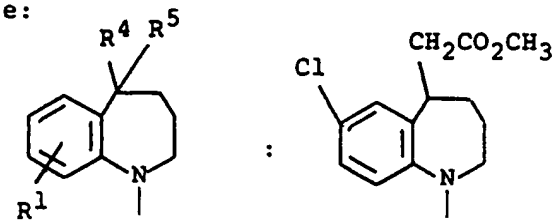
Crystalline form: Colorless amorphous

Form: Free

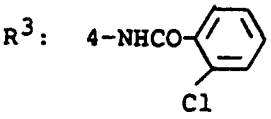
NMR analysis: 103)

Example 209

Structure:



R^2: 3-OCH_3



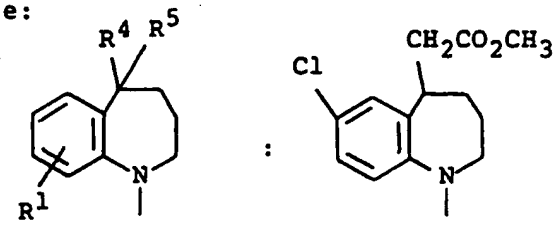
Crystalline form: Colorless amorphous

Form: Free

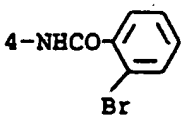
NMR analysis: 104)

Example 210

Structure:



R^2: 3-OCH_3

R^3: 

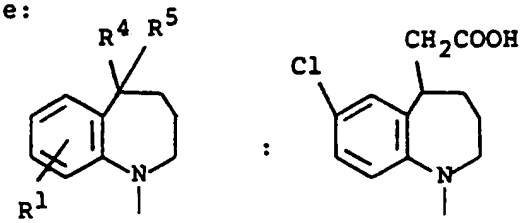
Crystalline form: Colorless amorphous

Form: Free

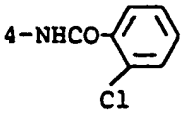
NMR analysis: 105)

Example 211

Structure:



R^2: 3-OCH_3

R^3: 

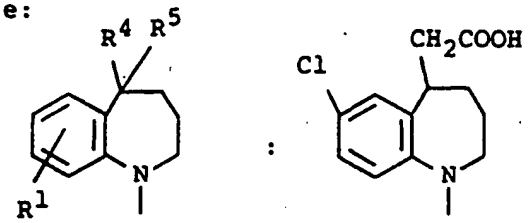
Crystalline form: Colorless amorphous

Form: Free

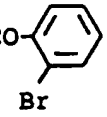
NMR analysis: 106)

Example 212

Structure:



R^2: 3-OCH_3

R^3: 4-NHCO- 

Br

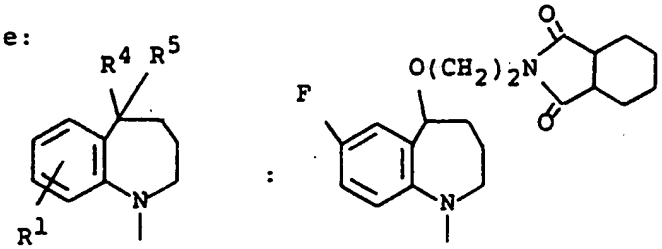
Crystalline form: Colorless amorphous

Form: Free

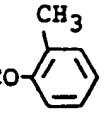
NMR analysis: 107)

Example 213

Structure:



R^2: 2-CH_3

R^3: 4-NHCO- 

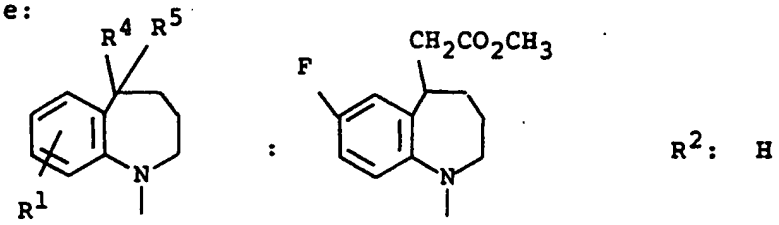
Crystalline form: Colorless amorphous

Form: Free

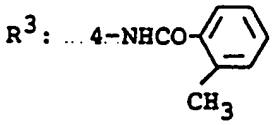
NMR analysis: 130)

Example 214

Structure:



R^2: H



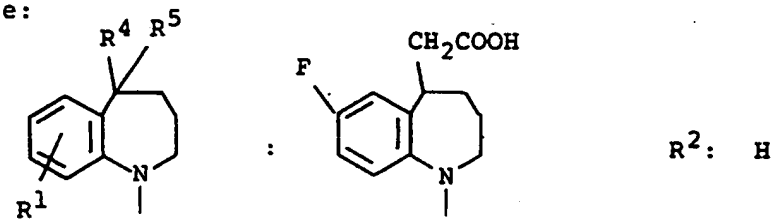
Crystalline form: Colorless amorphous

Form: Free

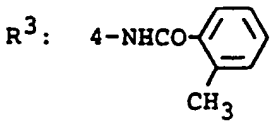
NMR analysis: 135)

Example 215

Structure:



R^2: H



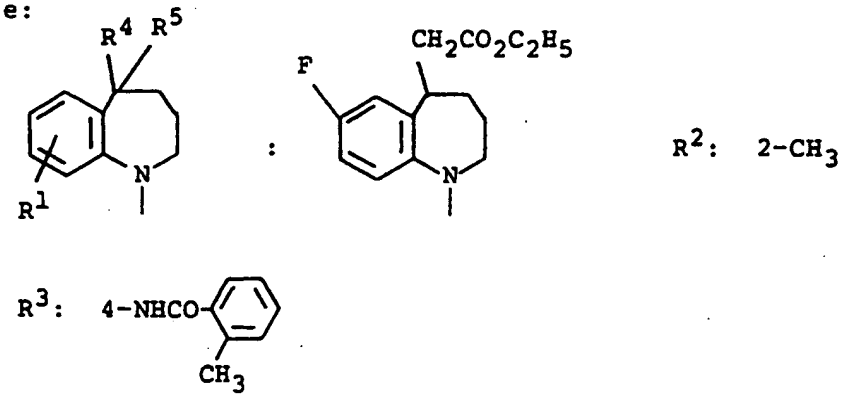
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 136)

Example 216

Structure:



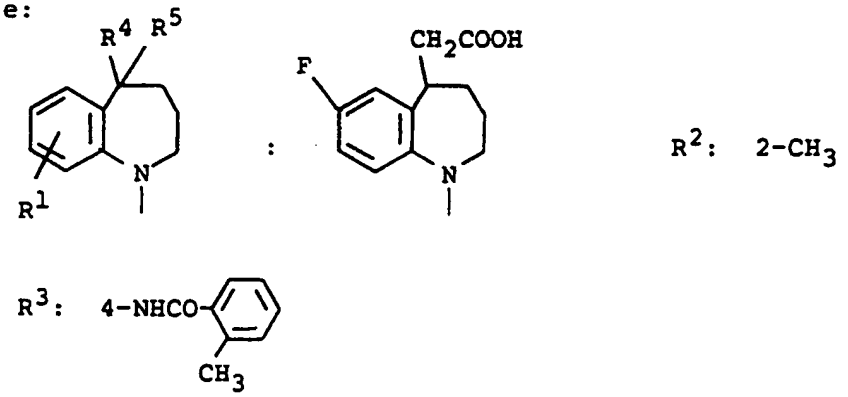
Crystalline form: Colorless amorphous

Form: Free

NMR analysis: 137)

Example 217

Structure:



Crystalline form: Colorless amorphous